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PANCREATIC COLLECTIONS (PSEUDOCYSTS) FOLLOWING PANCREATITIS AND PANCREATIC NECROSIS

Review and Analysis of Ten Cases

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IN reviewing the cases of so called pancreatic pseudocyst and suppurations at the San Francisco City and County Hospital, some interesting facts were brought out which merit consideration.

The work of Koerte, Lazarus, McWhorter, Opie, Judd, and many others has done much to pave the way for better understanding of the clinical and pathological findings in pseudocysts of the pancreas. Trauma, acute and chronic pancreatitis, and hemorrhagic necrosis have been associated with the development and formation of pancreatic pseudocysts and abscesses. The underlying cause of pancreatitis and hemorrhagic necrosis is still a subject of lively discussion, and it is far beyond the scope of this paper to delve into that phase except to mention some of the related conditions which may be closely associated with the pathogenesis of these cysts.

So called pseudocysts may be formed within the substance of the pancreas as the result of degenerative changes affecting the interstitial tissues of the gland, or adjacent to the pancreas when the corrosive action of the pancreatic ferments has led to the encapsulated accumulations about the gland. The greater proportion of these cysts is found lying within the lesser peritoneal sac and they usually present, according to Koerte, in one of three sites: (1) between the stomach and the transverse colon under the gastrocolic omentum; (2) between the stomach and the liver, under the gastrohepatic omentum; (3) between the leaves of the transverse mesocolon. Although these are the usual sites, many bizarre locations may be found. They have been known to dissect retroperitoneally and present in the pelvis.

The wall of the pseudocyst is formed by dense connective tissue of variable thickness. There is no true epithelial lining but often there is described an endothelial lining which apparently takes its origin from the connective tissue wall. The epithelial lining of the true cyst arises as the result of occlusion of a duct or by epithelial proliferation. It may be destroyed by the necrotizing action of the pancreatic ferment or by pressure necrosis, thus making differentiation between "true" and "false" cysts impossible.

Clinical and experimental evidence shows that cysts may be formed secondary to trauma of the pancreas. The history of trauma in cyst formation has been commented upon repeatedly in the literature since the days of Koerte, and appears to be associated with

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cystic development in 25 to 35 per cent of the cases, depending upon the author and the series quoted. Recent series are inclined to place the figure at 20 per cent or less. Apparently the resulting hemorrhage and trauma in or about the gland is the basis for development of the cyst. The secondary effect of necrosis and enzymatic changes due to liberated pancreatic ferments at the time of injury, or subsequently, may alter the contents of these cysts in such a degree that they may contain clear, straw colored, turbid or dark black fluid, and in addition may contain particles of sequestrated pancreatic tissue. True hematic cysts following trauma usually are nothing more than hematomas of the lesser bursa. They do not show the ravages of chemical alteration by the pancreatic enzymes. Lazarus, and Thiroloix and others have produced small cysts by trauma or by injecting necrotizing substances into the pancreas of experimental animals. There is little doubt then that both clinically and experimentally cystic accumulation may arise from traumatic injuries of the pancreas.

The relation of acute and chronic pancreatitis to the production of pancreatic cysts and suppurations is well established. No doubt this makes up a far greater proportion of the cases than formerly recognized. Both true and false cysts may result from pancreatitis. Just how this is brought about is the subject of considerable discussion. Tilger and Dieckhoff suggest that this may be the result of fibrosis throughout the various parts of the gland, constricting the ducts with partial obstruction and dilatation distally. This is followed by degeneration of the acinar cells which in turn leads to necrosis of other tissues by the action of the liberated ferments. Though this has never been proved experimentally, it seems perfectly logical that it may occur. Retention cysts apparently do occur as a result of partial obstruction of the pancreatic ducts either as a result of fibrosis, calculus, or tumor. Opie has shown that ligation of the main pancreatic duct in animals will not lead to the development of cysts but rather to resultant fibrosis and dilatation of the ducts distal to the site of occlusion; the so called ranula pancreatica of Virchow. Judd was of the opinion that all cases of pancreatic cyst are associated with pancreatitis. Although this may not always be the case, chronic pancreatitis frequently is found in association with pancreatic cysts. Which is the cause and which the effect is difficult to say, though it is reasonable to suppose from the clinical histories as well as from the pathological specimens of reported cases that the inflammatory process most probably precedes the cystic development.

Pseudocysts have been observed following hemorrhagic necrosis of the pancreas by a number of authors, including Francke, Rosenmorsky, Adler, Dressel, Carslaw, McWhorter, Judd and Wangensteen. Although the amount of pancreatic damage in hemorrhagic necrosis often is greater than in traumatic injury, the resulting collections would appear to develop quite comparably; that is, as the result of hemorrhage, necrosis, and enzymatic changes. The presence of pathogenic organisms, or biliary and duodenal content which may serve as the activating principle in the resulting hemorrhagic necrosis may bear some relation to the character of the accumulated fluid, suppuration being far more common in this group.

The frequent occurrence of biliary tract disease in association with pancreatic necrosis and pseudocyst as shown by Archibald, Opie, Judd, and others is of great significance. It was Archibald's contention that pancreatitis may be the result of bile entering the pancreatic duct and if this be true that subsequent pancreatic accumulations are the products of necrosis from bile pancreatitis. Judd reported 17 of 41 cases of pancreatic cyst which had associated biliary tract disease. Opie, Whipple, McWhorter, McPhedran, and many others have given sufficient clinical proof that biliary tract disease, with or without stones, and pancreatic disease can be closely correlated.

It may be difficult to differentiate at times between pancreatic cysts and pancreatic suppurations. Either may develop subsequent to trauma, hemorrhagic necrosis, or pancreatitis. The wall and contents of these cysts may be grossly indistinguishable, it being only a matter of degree of infection which separates the two types. Most writers on the subject believe that infection develops in these cysts sec-

ondary to tissue necrosis rather than after primary infection of the pancreas. In those cases of suppurative pancreatitis, the inciting organism in all probability is the cause of the pancreatitis as well as the suppuration. Archibald found that when infected bile was injected into the pancreatic duct it led to a more extensive necrotizing lesion of the pancreas than when bile alone was used and suppuration was far more frequent.

Pancreatic abscesses occasionally develop as a result of acute or chronic pancreatitis and usually in association with complete or partial obstruction of the pancreatic duct. The appearance of fat necrosis, inflammation, interstitial fibrosis, and hemorrhage in or about the gland, would lead one to believe that the origin of these abscesses is so closely akin to the other pancreatic collections which have been previously described that differentiation may be impossible.

Following the first episode of pancreatitis, the pancreas appears to be more vulnerable to recurrent insults, resulting in chronic pancreatitis. As a rule, cysts resulting from chronic pancreatitis contain clear or turbid fluid, often mucoid in character, whereas those resulting from acute pancreatitis or pancreatic necrosis have a tendency to be hemorrhagic in character, containing particles of tissue necrosis dispersed within its contents.

Since there seems no infallible way to differentiate, at laparotomy or necropsy, between hematogenic collections, pseudocysts, and pancreatic suppurations, the diagnosis and classification of these accumulations are subject to wide individual interpretation. It appears logical then, in view of what has been said, to disregard the term "false" or "pseudo" cysts and designate these as pancreatic cysts or collections resulting from trauma (direct or indirect), duct obstruction (calculi, tumor, inflammation), acute and chronic pancreatitis (infectious, chemical), and pancreatic necrosis (infectious, chemical, vascular). "Retention" cyst should be used to designate ductal dilatation arising secondary to partial or complete occlusion of the pancreatic ducts, whereas "true" cysts should be limited to denote those of a proliferative, hydatid, dermoid, or congenital origin.

The contents of these accumulations, as previously stated, may be old blood, clear or dark fluid, containing particles of necrotic débris. Trypsin, when present, renders proof that the collection is of pancreatic origin. The amylase content may be low, equal to, or, as often seen, markedly elevated as compared to the serum amylase level. If it is low or not above the corresponding blood level, its significance is doubtful. But if it is markedly elevated, it is significant and indicates that the collection is undoubtedly of pancreatic origin. It is true that in hematoma elsewhere in the body, in ascitic fluid, and in abscesses and other collections, amylase is contained in varying degrees but usually it closely approximates the serum amylase level. Gross discrepancies do not occur in accumulated fluid in the pancreatic region except in collections of pancreatic origin. It is well known that the amylase or lipase determination on proved pancreatic collections can be considerably below the level of the serum amylase. Opie states that they can be totally absent although we have not found this to be the case. Some writers have mentioned the significance of bile in the fluid, presuming that if bile is present it must have reached the pancreas by retrograde flow through the pancreatic duct, hence lending support to the theory of bile pancreatitis. Altered blood anywhere in the body cavity may give positive bile tests, so that the presence of bile in the cystic fluid is of no particular significance. Cultures of fluid from these collections often show growth of Bacillus coli and include other pathogenic organisms, streptococci, staphylococci, diphtheroids, and so forth. The frequency with which a positive culture is found depends to some extent upon the persistence with which it is sought.

COLLECTIONS SUBSEQUENT TO PANCREATIC NECROSIS

The first 6 cases to be reported are pancreatic accumulations resulting from acute pancreatitis and pancreatic necrosis. The first 4 cases are associated with biliary tract disease. In 1 of the 2 remaining cases no mention was made of the state of the biliary system in the operative report and no gall-bladder visualization was attempted. The other case sup-

posedly had a normal appearing biliary system at laparotomy and no underlying cause could be found for the pancreatic necrosis.

CASE 1. J.S., white American housewife, aged 21 years, entered the emergency ward of San Francisco Hospital with the story of indigestion, intolerance to fatty food, intermittent colic-like pain in the right upper quadrant for the past 14 months. The present illness began on the day before entry with severe abdominal pain which radiated to the back. Her condition on entry was fair. There was tenderness over the entire abdomen, with rebound tenderness in the upper quadrants, more marked on the left. The patient was found to have pelvic tenderness on rectal examination.

Her temperature was 102.4 degrees F. and the white blood cell count was 22,250. Because the patient had sustained high fever and persistent abdominal signs, she was operated upon 5 days after hospitalization with diagnosis of empyema of the gall bladder. Serum amylase on this day was 250 units.[1] The laparotomy showed fat necrosis and bloody fluid in the peritoneal cavity. The gall bladder, common duct, and pancreas were not drained. The abdomen was closed and the patient returned to the ward in fair condition.

After operation the serum amylase continued to rise and her clinical course grew considerably worse for the next few days. Six days after operation her serum amylase was 1050 units. Two weeks following surgery, gall-bladder visualization showed a well functioning gall bladder although many stones were seen. Gradually her fever subsided and she improved steadily although her postoperative course was interspersed with episodes of severe abdominal pain, leucocytosis, and marked elevation of serum amylase. Six weeks after entry she was reoperated upon. The gall bladder was removed and the common duct explored. No stones were found in the common duct. A large cystic mass, which lay behind the transverse colon, was found in the region of the body of the pancreas. This was marsupialized through the transverse mesocolon and the abdominal wall to the left of the umbilicus. The common duct was then drained through a T-tube. The postoperative course was moderately stormy. The cystic fluid had a dark brown color and contained necrotic flecks of tissue, was amylase-positive but contained no organisms on smear or culture. The cyst drained profusely for 6 weeks and then moderately for 4 weeks, and finally subsided completely. The serum amylase had returned to normal at this time. Although the cultures were negative for organisms at the time of operation, after the tube was inserted into the cystic cavity pancreatic drainage grossly was purulent within a day or so. It contained Bacillus coli on culture. Pathological sections of the gall bladder showed chronic cholecystitis, cholelithiasis, and hyperplasia of the regional nodes. Blood cultures were at all times negative. The patient was seen in the clinic 6 months after discharge, having no complaints.

[1]According to the method of Somogyi; normal range 60 to 180 units.

CASE 2. J.H., 57 year old male steamfitter, entered San Francisco Hospital with the story of having right upper quadrant pain with jaundice intermittently for the past year. Seven or 8 weeks previous to entry into the hospital the pain became quite severe and increased in intensity. Three days before entry he had a sudden onset of knife-like pain in the abdomen, radiating to the left shoulder. A second severe attack occurred on the day of entry with severe pain radiating to the right groin from the midabdomen. Abdominal examination showed marked guarding, spasm, with rebound tenderness in the left upper quadrant. The temperature was 99.2 degrees F. and the white blood cell count was 18,250. Urine contained three plus albumen and a trace of sugar. Serum amylase was 193 units. Icterus index was 10.4 Roentgenograms showed a loop of distended small bowel, presumably duodenum, which may have been slightly enlarged. Gallbladder visualization attempted on two occasions failed to show any dye, and no stones were seen. Two days after entry a mass was palpated in the right upper quadrant. The temperature gradually fell, and the white blood cell count ranged from 12,000 to 18,000. The patient was operated upon with the diagnosis of acute obstructive cholecystitis. When the peritoneal cavity was opened a large quantity of clear yellowish, ascitic fluid was found. A large fluctuant mass was found in the region of the head of the pancreas which appeared reddish-blue in color and had a thick wall. It was aspirated and 2,000 cubic centimeters of greenish-brown material was removed which contained flecks of fibrin and necrotic material. The amylase content of this fluid was 475 units. The cyst wall in places was 3 to 4 centimeters in thickness. The cyst was marsupialized through the laparotomy incision. Biopsy of the cyst wall showed chronic inflammatory tissue. The condition of the gall bladder was not noted at the time of operation. Smears and culture of the cystic fluid were reported negative at first, but later Staphylococcus albus was reported. The fluid was turbid and contained many polymorphonuclear and plasma cells. After operation the serum amylase ranged from 14 to 71 units on repeated occasions. Excoriation of skin about the drainage site was slight. Three months after discharge from the hospital he was feeling well and drainage had ceased.

CASE 3. D.G., 45 year old American housewife, with history of intermittent pain in right upper quadrant with jaundice for 2 years. The week before entry she had a sudden onset of severe pain in the right upper quadrant and pain in the pit of her stomach. She felt cold and perspired profusely. When she was brought into the emergency ward of the San Francisco Hospital her temperature was 99.6 degrees F. and the white blood cell count was 26,000. Abdominal examination showed a mass 10 centimeters in diameter projecting downward from the midline. There was tenderness over the entire ab-

domen and especially in the left upper quadrant. The impression at that time was empyema of the gall bladder or pancreatic cyst. Gastrointestinal series showed a wide duodenal loop compatible with enlargement of the head of the pancreas. At laparotomy 8 days after entry, fat necrosis was seen and a cystic mass was found in the region of the lesser bursa. The transverse mesocolon was pushed upward by the mass. By blunt dissection the cyst was opened through the transverse mesocolon. When its cavity was entered, a large amount of dark purulent material was removed, the exact amount was not noted. This fluid contained a large amount of necrotic tissue, presumably pancreatic in origin. No smears or cultures were taken of the material nor were amylase studies made. The cyst was drained and the wound was closed. The patient ran a rather stormy postoperative course for a day or two but on the third postoperative day the temperature was normal and it remained so. After draining moderately for 6 weeks the cavity closed and the patient was discharged as well. No mention of the gall bladder was made in the operative note.

Ten years later, in 1940, she was readmitted with pain in the right upper quadrant, a palpable tender mass and jaundice. Icterus index was 40 upon entry and serum amylase 70 units, blood sugar 202 milligrams per cent. Diagnosis of acute cholecystitis was made and the patient was operated upon. The gall bladder was found distended and filled with many stones. The common duct was explored, but no stones were found and no dilatation of the duct was noted. Many adhesions were found in the region of the gall bladder, duodenum, and pancreas, fixing them to the old incision of the abdominal wall. The pancreas did not appear abnormal at this time. Sections of the removed gall bladder showed chronic cholecystitis, and multiple calculi were found in the gall bladder. The patient was discharged from the clinic 6 months later, her diabetes being controlled with small doses of insulin.

CASE 4. G.A., 57 year old male mechanic, with history of onset of acute abdominal pain 4 days before entry. The pain originated in the epigastrium, traveling toward the left flank. He vomited a small amount of greenish material. The patient stated that he had a similar attack 5 years before. His temperature was 101 degrees F. and the white blood cell count of 11,000 had a normal distribution. The abdomen was tender to deep palpation but no masses were felt. The temperature and white blood cell count dropped to normal shortly after entry. The man complained of severe abdominal pain with radiation of pain into the right testicle for the next one or two days. Then the pain gradually subsided and he improved. Ten days after entry a mass became palpable in the right upper quadrant. Gastrointestinal series showed a very wide duodenal loop compatible with enlargement of the head of the pancreas. The gall bladder was not visualized. Blood sugar was within normal limits. Three weeks after entry, at operation, a large mass in the pancreatic region containing necrotic tissue, blood, serum, and fibrin was drained. Fat necrosis was evident. Cultures of the material showed Bacillus subtilis. The patient expired suddenly the following day. Autopsy showed congenital absence of the gall bladder with a stone in the common duct. Between the liver, pancreas, and the stomach and beneath the transverse mesocolon was a large necrotic mass of tissue and fibrin. A large cystic cavity filled with dark blood was found in the head of the pancreas. A similar but smaller cyst was found in the body of the pancreas. Microscopic sections of the region about the pancreas showed necrosis, lymphocytic infiltration, with marked fatty degeneration. No normal pancreatic tissue was seen.

CASE 5. A.H., 58 year old white American carpenter, entered San Francisco Hospital 2 months after onset of severe upper abdominal pain. The initial pain was so severe that he was forced to get off the train on which he was traveling and seek medical relief. The pain and vomiting continued for several days then gradually subsided, but he noticed a persistent, dull cramping pain in the epigastrium which was aggravated by eating. One month prior to entry into the San Francisco Hospital he had another severe bout of pain which lasted only a few hours. The patient lost a considerable amount of weight during this period of time but denied being jaundiced. Physical examination on entry revealed an emaciated man having a mass in the upper part of his abdomen which measured 10 by 16 centimeters, was smooth, globular and gave the impression of being cystic in nature. Peristalsis was visible from the left to the right in the upper quadrants over the mass. Gastric analysis showed 10 degrees as the highest total acid. Serum amylase was 222 units on entry. Glucose tolerance test was within normal limits. Gastrointestinal series showed no evidence of intrinsic gastric lesion. The stomach was encroached upon by a large mass and the duodenal loop was enlarged. Diagnosis of pancreatic cyst was made. At operation a large mass was found behind the transverse mesocolon. This was marsupialized at the site of the abdominal incision. There was evidence of extensive fat necrosis. The gall bladder could not be felt. A week later the cyst was drained by a trocar at the site of marsupialization and 550 cubic centimeters of dark brown fluid was removed. The material, which was filled with flecks of necrotic débris, had a specific gravity of 1.014 and contained many white and red blood cells. Smears showed gram-negative rods and, on culture, the Bacillus coli was found. The fluid contained 5,595 units of amylase. The blood amylase level remained slightly elevated for several weeks, gradually coming down following drainage of the cyst. At no time did this patient run more than 1 degree of fever. The white blood cell count was never above 9,000. The patient improved gradually. There was a considerable amount of digestion of tissue about the sinus opening for several weeks. The cyst drained for 6 months but finally closed. Six months after drainage had ceased, gas-

tric pneumograms showed a residual mass in the region of the pancreas which displaced the stomach upward. Gastrointestinal series showed a widened duodenal loop. Cholecystograms showed good concentration of the dye and no stones. A year later a small ventral hernia was repaired which had developed at the site of drainage. At that time gastrointestinal series was reported negative and no calcifications were noted in the region of the pancreas. In repairing the hernia, the peritoneum was opened and the abdomen was explored. Many adhesions were found and a small hard noncystic mass was felt in the region of the pancreas which was thought to be the vestige of the previously drained pancreatic cyst. The patient is asymptomatic at the present time and no definite mass can be felt on abdominal palpation.

CASE 6. B.W., 34 year old American housewife. Five days before entry the patient had severe abdominal pain and diarrhea. She was taken to a private hospital where morphine sulfate was given to control the pain. Subsequently she was removed to the San Francisco Hospital with the diagnosis of acute cholecystitis. During the 6 months prior to entry the patient had noted that fatty food and starches made her nauseated. Since that time once or twice a week she has had episodes of sharp colic-like right upper quadrant pain which lasted for as long as 1½ hours. Her present attack was similar to the previous attacks but was more severe. On entry she was not in great distress. Abdominal examination showed a mass in the right upper quadrant which was very tender. Her temperature was 101 degrees F., the white blood cell count was 8,500, and the icterus index was 15.5. The blood sugar was normal, and bile was found in the urine. She was operated upon 6 days after onset of pain with diagnosis of acute cholecystitis. When the abdomen was opened bloody fluid was discovered in the peritoneal cavity, fat necrosis was present in the region of the pancreas. There was a cystic mass containing about 60 cubic centimeters of dark brown fluid in the region of the lesser bursa which was drained through a stab wound. The pancreas was hard, swollen, and indurated. The gall bladder was of normal size and consistency. The patient drained purulent material after operation, but cultures and smears of this material were negative. The patient continued to run a low grade fever and an elevated white blood cell count after operation for several weeks. A month later she was reoperated upon. A mass about 10 centimeters in diameter was found just lateral to the sinus tract which, on aspiration, yielded 200 to 300 cubic centimeters of pus mixed with necrotic tissue. This abscess apparently was localized at the site of the previously drained pancreatic collection. Drainage of this abscess continued for a month or 6 weeks. The patient made an uneventful recovery. Smears and cultures which were obtained of the cystic fluid at the second operation showed Streptococcus viridans, Staphylococcus albus, and gram positive rods, presumably Bacillus coli.

COLLECTIONS SUBSEQUENT TO SUPPURATIVE PANCREATITIS

The following 2 cases are illustrative of pancreatic suppurations. The first case most likely resulted from septic hemorrhagic pancreatitis. The second case appears to be one of acute and chronic pancreatitis with partial obstruction of the pancreatic duct with suppuration developing distal to the site of obstruction. Why this does not occur more commonly as we see in obstructions of other glandular structures (kidney, liver, etc.) is a question. Perhaps it is due to the bacteriostatic action of the pancreatic (proteolytic) enzymes.

CASE 7. H.S., a 20 year old American married housewife, entered San Francisco Hospital with the history of abdominal trauma sustained many years before. The patient had been drinking heavily and quite suddenly on the day of entry developed severe abdominal pain. She was brought to the emergency ward of the San Francisco Hospital in mild shock. She was vomiting and appeared acutely ill. Blood pressure was 105/70, temperature 99.6 degrees F. The upper abdomen was markedly guarded to palpation. Roentgenograms were negative for free air in the peritoneal cavity. The white blood cell count was 9,800, and the urine was negative. After observation the patient was sent to the medical ward with a diagnosis of possible alcoholic gastritis. In the medical ward her temperature rose to 102 degrees F. and the serum amylase showed 297 units, the white blood cell count was 21,000. The Wassermann reaction was negative. Agglutinations for typhoid, paratyphoid A and B, and undulant fever were all negative. Gall-bladder studies were not made. Shortly after admission she developed alcoholic hallucinations and was sent to psychopathic ward for 5 days where she continued to have a high fever. Daily determinations of serum amylase during this time varied from 297 to 313 units. Her abdominal findings persisted and she was returned to the medical ward. She appeared acutely ill, her temperature was elevated and her white blood cell count fluctuated between 12,000 and 13,000 for the next few days. Gastric pneumograms taken 2 weeks after entry showed a space-occupying lesion behind the stomach and in front of the lumbar vertebrae, "presumably a pancreatic cyst." The patient was taken to surgery and, through a midline incision, the abdomen was opened. There was no evidence of fat necrosis. A large, bulging mass presented itself beneath the transverse mesocolon which was entered through the incision in this structure. The contents of the mass contained frank pus and particles of necrotic tissue. The remaining pancreatic tissue was palpated through the cavity and was found to be stony hard. The cyst was explored and found to be multilocular. On its being converted into a single cavity, fragments of

necrotic tissue were removed. The cyst was marsupialized and drained through the incision. The patient made an uneventful recovery. Smears made from the contents showed no bacteria but Bacillus coli were cultured. Determinations of the fluid showed it to contain 5,000 units of amylase. The patient developed a secondary collection in the right lower quadrant which, on drainage 10 days later, showed thick purulent material containing Bacillus coli and which had an amylase reading of 682 units. Serum amylase prior to the drainage of the second abscess was 192 units. The patient was discharged 6 weeks after the second operation with slight drainage from both wounds. The blood sugar was not elevated. She has since recovered completely.

CASE 8. A.W., 75 year old American housewife, for the past 10 years had complained of intermittent episodes of abdominal pain. Her present illness began similarly to previous attacks 3 days prior to entry in San Francisco Hospital. She complained of generalized abdominal pain, nausea but no vomiting. She had had no bowel movements for 2 days. Her temperature was 101 degrees F. and the white blood cell count was 20,000. There were no abdominal masses although she was tender throughout the upper abdomen. Urine was negative except for a trace of albumen. Barium enema on entry showed diverticulitis of the colon. A flat plate of the abdomen showed no definite obstruction of the small bowel. The patient was operated upon 5 days after entry with the diagnosis of possible bowel obstruction. Many adhesions were found but no obstruction of the bowel was encountered. Because of her poor condition during the operation, a rapid closure was made without a definite diagnosis being made. She died 48 hours later. Autopsy showed acute suppurative and chronic interstitial pancreatitis. Fat necrosis was evident throughout the pancreatic area. She had a small left subphrenic abscess, chronic cholecystitis and cholelithiasis. An islet cell adenoma of the pancreas was an incidental finding. No cultures of the pus were obtained at autopsy.

COLLECTIONS SUBSEQUENT TO CHRONIC PANCREATITIS

The last 2 cases to be reported are presumably pancreatic accumulations following chronic pancreatitis. Both of these patients had long histories of repeated episodes of epigastric and abdominal pain suggestive of chronic pancreatitis. Case 9 apparently resulted from chronic pancreatitis with the cyst lying within the glandular substance distal to the site of partial obstruction of the duct. Case 10 showed pancreatic calcifications associated with chronic pancreatitis. Duct calculi as well as interstitial calcifications were reportedly found at the time of operation. The pancreatic collection at the time of surgery was found to lie distal to the site of calcification.

CASE 9. C.C., 54 year old white American male shipyard worker, entered the hospital with a 10 year history of intolerance to fatty food and indigestion. One and one-half years ago the patient was seen in the San Francisco Hospital with abdominal pain which subsided soon after entry and he was discharged to the out patient clinic. Five weeks before entry he began having epigastric discomfort, nausea, and gradual development of an abdominal tumor. At the time of entry a large mass, 8 by 10 centimeters, was palpated in the right upper quadrant which extended to the left of the midline. A fluid wave was present. The patient was afebrile, and his white blood cell count was 13,000. His serum amylase was 335 units and the fasting blood sugar was 103 milligrams per cent. Cholecystograms showed normal filling and no evidence of stones. Roentgenograms of stomach and duodenum showed a large mass posterior to the stomach pressing downward on the transverse colon. Four days after entry exploration through a left upper quadrant rectus incision revealed a small amount of clear yellow peritoneal fluid and a large dark blue cystic mass under the gastrocolic ligament. On aspiration of the cysts, 4 liters of brownish fluid was obtained. The wall of the cyst was composed of chronic inflammatory tissue. Cultures and smears of the cystic fluid were negative for bacteria. No bile salts were present in the cystic fluid and its amylase content was 85 units. After operation a moderate amount of clear yellowish, mucoid material drained from the cyst. No evidence of skin digestion was noted about the sinus opening. The patient was discharged much improved a few weeks later with a draining sinus which became obliterated approximately seven weeks after operation.

CASE 10. G.G., 39 year old white American salesman, entered San Francisco Hospital with the complaint of abdominal pain and vomiting for one week. The patient gave a history of frequent attacks of epigastric pain for many years. He was moderately sick with temperature of 100.6 degrees F. and a white blood cell count of 17,000. Abdominal examination showed moderate distention with marked epigastric tenderness. Rectal tenderness was also present. Roentgenograms showed no free air in the peritoneal cavity. The urine was negative, and the serum amylase was 417 units. On the following day it was 820 units. The clinical course improved after entry into the hospital, despite the rise in serum amylase. The patient was discharged to the out patient department but failed to return. Two and a half months later a similar episode of abdominal pain with vomiting led to his re-entry into the hospital. Abdominal examination showed generalized pain and tenderness and a mass approximately 8 by 12 centimeters could be discerned in the left upper quadrant. Serum amylase on entry was 327 units. Urine was negative. The blood contained 14,500 white cells. Roentgenograms of the abdomen showed

TABLE I.

Case No.	Serum amylase readings—units	Days preoperative	Cystic fluid amylase—units	Serum amylase readings—units	Days postoperative
1	197	21	Positive for amylase	337	2
	455	18			
	351	10			
	185	5			
	488	2			
2	193	6	475	71	6
				14	26
5	297	14	5,000	192	5
	273	4		107	22
Secondary collection drained					
	192	35	638		
	107	18			
6	222	28	5,595	214	10
				395	35
				240	42
8	425	4	85	169	2
	237	2		175	7
				307	21
9	327	8	Not tested	58	4
	365	1		133	14

a calcification in the right upper quadrant, presumably in the region of the gall bladder. Cholecystograms, however, were essentially negative, and no stones were seen. The calcification was thought to lie within the pancreas. Pneumograms of the stomach showed a large retroperitoneal mass in the region of the pancreas pushing the stomach forward. A week after entry the patient was operated upon through a left upper oblique subcostal incision. The abdomen was opened and 300 to 400 cubic centimeters of old bloody fluid was found. Numerous areas of fat necrosis were seen. A large cystic cavity composed partly of bloody fluid and partly of pancreatic tissue apparently had ruptured a short time before operation when the patient had experienced severe pain early in the morning. Exploration of the cystic cavity showed the pancreas to be hard, sclerotic, and containing a firm mass which, when excised, was found to contain much scar tissue and one large and several small calcareous deposits. The major portion of the scar and the calculi were removed. The area was drained. The patient made a satisfactory convalescence. Serum amylase at the time of surgery was 54 units. Four days after operation the draining fluid contained 20 units of amylase whereas the serum amylase was 58 units. Biopsy of the cyst wall showed chronic pancreatitis with metaplasia of pancreas of epidermoid, ductular character. The wall of the cavity was composed of inflammatory connective tissue. At first there was a great deal of skin irritation and necrosis about the sinus tract opening. When last seen in the clinic the patient appeared much improved although there was a small amount of drainage from the sinus.

These 10 cases serve to illustrate some of the frequent types of pancreatic cysts of pancreatic accumulations resulting from pancreatitis and pancreatic necrosis. Although we have no cases resulting directly from trauma, it cannot be denied that this is a relatively frequent cause but probably less common than formerly thought.

In 3 of our cases no known cause could be established for the underlying pancreatic disease although in 2 of these cases the possibility of gall-bladder disease could not be ruled out from the information derived from the records. Of the remaining 7 cases, 6 were associated with biliary tract disease and 1 with acute alcoholism.

Cultures were taken of the cystic fluid of 7. Four showed growth of organisms, 2 containing Bacillus coli, 1 Bacillus subtilis, and 1 Staphylococcus albus. Two cases had negative cultures but the immediate postoperative drainage from the collections were grossly purulent. This shows a comparatively high incidence of infection.

In all but one, fat necrosis was found at the time of surgery even though in some cases there was a lapse of several weeks between the onset of the disease and the time of laparotomy.

Much has been written about the value of the serum amylase test in pancreatic disease yet we must confess ignorance as to how and when it increases during the acute phase of the disease. Six of our cases, as tabulated in Table I, have interesting amylase readings of the cystic fluid as well as of the serum before and after drainage of the resulting collection. It is interesting to note how promptly the serum amylase dropped following drainage of the cysts in 4 cases whereas in 2 cases it remained elevated above normal for several weeks. Apparently the serum amylase level has no direct relation to the amylase content of the cystic fluid, as may be noted in Table I.

Although it has been said that chronic pancreatitis usually does not give a sustained elevation of the serum amylase, it may be worthy of note, in view of our findings, that a sus-

tained elevation of the serum amylase is suggestive of the presence of a pancreatic collection. The elevated serum amylase most likely results from the pancreatitis associated with the pancreatic accumulation rather than directly from absorption of the cystic contents. This bears further clinical observation and, if true, may aid materially in early diagnosis of pancreatic collections.

Rupture of these accumulations is said to be relatively rare and often fatal. It occurred in only 1 of our cases although several patients had peritoneal fluid and associated fat necrosis. This patient (Case 10) survived although he had a stormy postoperative convalescence. Two cases developed subsequent collections following primary drainage, either as a result of leakage of the cystic fluid into neighboring areas or incomplete drainage of the accumulation at the first operation. Many of the accumulations are loculated, and it is surprising that subsequent collections do not occur more frequently. To date we have no known recurrences following drainage. In only 2 cases was there associated jaundice with the pancreatic accumulations. One of these cases had concomitant gall-bladder disease with stones while the other apparently had a normal biliary system. The jaundice in this case was either due to obstruction of the common duct by external pressure or possibly was the result of absorption of the pancreatic hematoma incident to the pancreatic hemorrhage and necrosis.

We have no known cases of spontaneous internal drainage either into the bowel or pancreatic duct.

Diabetes as a complication of pancreatic insufficiency due to necrosis is reported as found in 5 to 8 per cent of such cases. In 1 of our cases (Case 3) the patient had no glycosuria during her original hospitalization for pancreatic necrosis and drainage of the pancreatic collection. However, 10 years later when she re-entered the hospital for cholecystectomy for chronic cholecystitis and cholelithiasis she had mild diabetes with fasting blood sugar of over 200 milligrams per cent. Two other patients developed transient glycosuria during the acute stage of their disease but it disappeared following drainage of the collection. One patient developed a small incisional hernia at the site of marsupialization of the cyst. This was repaired a year and a half later, approximately a year after the drainage had ceased. It healed without complication.

Five of the 10 cases had known gall-bladder disease. In 3 of the other 5 cases no mention of the biliary system was made in the record of findings at operation and no subsequent cholecystograms were made. These figures compare favorably with other series and again serve to remind us of the frequency of associated biliary tract disease and pancreatic disease.

The symptoms of pancreatic accumulations are not specific. There may be a prolonged history of indigestion and abdominal discomfort not unlike that of cholecystitis, peptic ulcer, or of many diseases of the upper abdomen, or they may develop suddenly following an acute pancreatic insult. Although the pain often is the presenting symptom along with the development of an abdominal mass, it may be totally absent. As the tumor increases in size the pain usually becomes more severe. With repeated hemorrhages into the cyst, as frequently happens, nausea vomiting and acute pain may be experienced. During one of these episodes the diagnosis of biliary tract disease or perforated ulcer may be made, only to find at laparotomy a pancreatic collection with evidence of recent hemorrhage in or about its contents. In 4 of our cases the preoperative diagnosis of cholecystic disease was made, although at laparotomy a hemorrhagic pancreatitis with hematic collections was found. It is most difficult to differentiate the two diseases because of the similarity of the objective and subjective complaints of the patient and the frequent association of biliary tract disease with pancreatic disease.

Two patients in our series gave rather typical histories and were found to have classical findings of pancreatic cysts, presumably on the basis of chronic pancreatitis. They had had intermittent episodes of abdominal pain over many weeks or months associated with the gradual development of an abdominal mass. Roentgenograms and amylase tests aided in their diagnosis. Of the 4 remaining cases, one patient was operated upon for

acute bowel obstruction but later at postmortem examination suppurative pancreatitis was found. The 3 remaining cases were suspected of being pancreatic cyst preoperatively, a suspicion which was substantiated at laparotomy.

A sudden enlargement of the cyst with appearance of shock and intense pain may be produced by massive hemorrhage into the cyst; or sudden diminution in the size of the cyst with associated diarrhea, shock, and a rigid abdomen may be the result of rupture of the cystic contents into the bowel or free peritoneal cavity. Excess fat is often found in the stool in cases of pancreatic cysts but foamy stools are a rarity.

Little can be added to the long list of diagnostic procedures that have been described repeatedly in the literature. A fact worthy of mention, however, not previously stressed in the literature, is the frequency with which hemorrhagic necrosis and pancreatitis precede the onset of pancreatic collections. No doubt many small collections and hematomas which escape clinical detection are spontaneously absorbed. By careful examination, undoubtedly many more of these could be diagnosed.

Roentgenographic examination is a valuable adjunct to our diagnostic procedures. A flat plate of the abdomen may show a silhouette of the cyst. Barium meal may denote the displacement of the stomach by the mass, and the duodenal loop may be widened because of enlargement of the head of the pancreas. Barium enema may show the colon displaced in various directions or encroached upon by the pancreatic tumor. Outlines of the cyst wall by lipiodol injections into the sinus tract following drainage occasionally have been resorted to in cases of retention cysts with duct obstruction. Recently gastric pneumograms have been taken in several of our suspected cases of pancreatic cysts with notable success. Using a modification of the method of Engel and Lysholm, our radiologists at the San Francisco Hospital on several occasions have demonstrated retrogastric enlargements of pancreatic origin that could not have been identified otherwise. The posterior gastric wall of the air-distended stomach was thereby used to delineate the pancreas and the retrogastric tissue. It has been shown with marked regularity that when the thickness of the retrogastric tissue was greater than the width of the vertebral body, the pancreas or the retrogastric tissue was abnormally enlarged. Despite all these diagnostic procedures, often the diagnosis cannot be made preoperatively with certainty.

SUMMARY

Ten cases of pancreatic collections have been presented.

An attempt has been made to classify pancreatic collections on an anatomical as well as on a pathological basis. Since no valid differentiation can be made between "hematic" cysts, "pseudo" cysts and necrotic suppurations, they should be referred to simply as collections secondary to pancreatic trauma, inflammation, or necrosis.

The term "retention" cyst should be used to designate cystic dilatations arising secondarily to partial or complete occlusion of the pancreatic ducts. "True" cysts should be limited to denote those of proliferative (neoplastic), hydatid, or congenital origin.

Numerous amylase determinations were made of the serum as well as of the cystic fluid in 6 cases. As will be seen, there appears to be no quantitative relationship between the serum and the cystic fluid amylase, either before or subsequent to drainage of the accumulation.

Persistent elevation of the serum amylase following the signs or symptoms of pancreatitis or pancreatic necrosis is significant, indicating the probable development of a pancreatic collection.

The differential diagnosis of pancreatic accumulations from biliary tract disease, perforated ulcer and neighboring pathology may be difficult.

Gastric pneumograms were found to be of material aid in the diagnosis of retrogastic and pancreatic enlargements.

Satisfactory results were attained in all of our cases by single drainage or marsupialization of the pancreatic collection.

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STRENGTH FREQUENCY CURVES IN ELECTRODIAGNOSIS OF EXPERIMENTALLY PRODUCED PERIPHERAL NERVE LESIONS IN THE CAT

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PHYSIOLOGISTS have been interested in the stimulation of nerves and muscles with alternating currents of variable frequencies since Nernst pointed out, on the basis of his polarization theory, that the ratio between the square of the intensity and the frequency was a constant.

On the other hand, the results of stimulation of nerve and muscle by alternating current have not been employed as indications of the state of the nerve-muscle complex in disease or injury to the peripheral nervous system.

There are two observations which have been made by physiologists which are related to the use of the alternating current as an electrodiagnostic procedure. They are (1) the so called optimum frequency or pararesonance and (2) the discontinuity of the strength frequency curve when large fluid electrodes are employed.

As the technique for generating sine waves improved, the use of lower and lower frequencies was made possible and this permitted Lullies, Achelis, and Renqvist and Koch to point out that the strength frequency curve shows a point at which at a certain frequency a minimum current is necessary for stimulus. This optimum frequency was said to be situated around 100 cycles per second. This is said to be analogous to the resonance point found in the tuning of electromagnetic oscillations. In order to avoid any confusion with the definition as used in electronics, Monnier proposed for this optimum frequency the term, pararesonance. Since the components of the electrical circuits in biological tissues are not fully known, we elect to use the term "optimum frequency."

Although when, in the case of the frog's nerve, the threshold voltage is plotted against the logarithm of the frequency, the curve is said to be U-shaped and the two branches are symmetrical about a vertical axis passing through the optimum frequency, it will be seen that using larger electrodes and percutaneous stimulation in the case of the cat, a different type of curve was obtained.

It was to be expected that the discontinuity found in the strength duration curves when large fluid electrodes were used (Lucas, Davis, Watts, and Rushton), and which represent the separate stimulus characteristics of nerve, muscle, and myoneural junction, would be found in strength frequency curves. Coppee pointed out that in the case of a toad's sartorius muscle, stimulated under Ringer fluid with large electrodes, the strength frequency

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curve shows two parts, each of which presents a minimum. One lies at 120 cycles per second and corresponds to the optimum frequency of the motor nerve of the sartorius. The other minimum is located a little below one cycle per second. The strength frequency curve no longer shows an axis of symmetry.

Adrian observed that curves obtained by plotting the relation between strength and duration of current necessary to excite muscles during regeneration and degeneration of its nerve supply are complex and that "these complex curves are found in every case which does not give either the simple curve with the short chronaxie, typical of intact muscle (.0005 second or less) or else the simple curve with the long chronaxie of denervated muscle (.008 second or more)." Such complex curves permitted the recognition of the existence of function of nerve during a period of degeneration and its return with regeneration.

Among other things, we will here report upon similarly complex strength frequency curves during degeneration and regeneration, and continuous ones during denervation and in the normal state.

METHOD

Apparatus. Two electronic beat frequency oscillators were employed at various times as the sources of alternating current for the percutaneous stimulation of the animals. One of the oscillators was especially designed for low frequencies, while the other was suitable for the higher frequencies. The output from the high frequency oscillator was fed into a low distortion power amplifier which was provided with an output transformer and resistive attenuator capable of handling far more power than was required in the actual stimulation. Calibration of the beat frequency oscillators was used to give the indication of frequency of the stimulating current.

The root mean square value of the stimulating current was measured by means of a Weston model 301 milliammeter (rectifier type) which had been provided with a compensating network and a special calibration that rendered it accurate. For the band of frequencies between 0.75 cycles per second and 0.08 cycles per second, a commercially available mechanical sine wave generator was employed. Since the meter on this instrument indicated crest values of current, it was necessary to convert these readings to root mean square values for the illustrations.

Before the examination, the site over which the electrodes were to be placed was first pricked deeply by a needle five times and vigorously rubbed with electrode jelly to minimize cutaneous resistance; the indifferent electrode, measuring 2 centimeters in diameter, was placed over the lateral portion of the Achilles tendon. The exploring electrode, measuring 1.5 centimeters in diameter, was placed in the middle and lower part of the popliteal fossa. The electrodes, which were circular, were constructed of copper and covered with chamois; they were immersed in salt solution for 15 minutes prior to use and then covered with electrode jelly.

Threshold amperage was determined by first setting the dial of the oscillator at the desired frequency, then by means of a potentiometer, the current was increased from zero until tetanus was observed.

The material consisted of 10 normal cats and 5 cats in which a section and immediate suture of the sciatic nerves were done, and 3 animals in which after a long segment of the sciatic nerve was removed, the proximal stump was injected with alcohol to discourage regeneration.

RESULTS

The strength frequency curve in the normal cat. When percutaneous stimulation as above described was used, the strength frequency curve obtained for the gastrocnemius muscle in the normal cat was found to be a continuous one. Since, because of the pain produced, in most instances, it was necessary to anesthetize the animals in which nerves had been sectioned; the conditions for the anesthetized and unanesthetized normal animal will be described. In the unanesthetized normal animal, the average amperage at 20 cycles per second was 0.3 milliampere; at 40 cycles per second, 0.3 milliampere; at 60 cycles per second, 0.32; at 100 cycles per second, 0.33; and 500 cycles per second, 0.35 milliampere; at 1000 cycles per second, 0.5 milliampere; at 2000 cycles per second, 0.75 milliampere; at 3000 cycles per

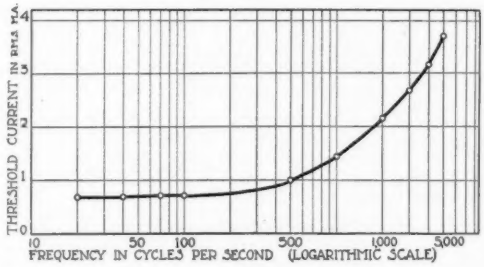

Fig. 1. Threshold current versus the frequency of the alternations in anesthetized normal cat. Each point is an average of data from 10 animals.

second, 1.0 milliampere; at 4000 cycles per second, 1.58 milliamperes; and at 5000 cycles per second, it was 2.0 milliamperes. It is well to note at this point that all examinations with frequencies below 20 cycles per second (0.75 cycles per second to 0.08 cycles per second) were made on the unanesthetized animals.

In the case of the anesthetized normal animal, the values were higher, thus at 20 cycles per second, the amperage was 0.75 as compared to 0.3 milliampere in the unanesthetized animal; at 5000 cycles per second, it was 3.7 milliamperes as compared to 2.0 milliamperes in the unanesthetized animal (Fig. 1); the form of the curves in the two was similar. In neither did we find the optimum frequency to be 100 cycles per second, but a wide band from 100 to 20 cycles per second, wherein there was a very small change in amperage, but nevertheless a measurable diminution down to 20 cycles per second. At sometime between 20 cycles per second and one cycle per second the amperage rises slightly, but at 0.75 cycle per second the average amperage was only 1.1 milliamperes and at the very slow frequency of 0.08 cycle per second, only 1.3 milliamperes. It may be seen that using percutaneous stimuli through larger electrodes the band of optimum frequencies is between 20 and 1 cycles per second and the two branches of the curve are asymmetrical.

The changes from normal of the strength frequency curve during degeneration, denervation, and regeneration consist in changes in (1) threshold current at various frequencies; (2) shifting of the band of optimum frequencies; and (3) discontinuities in the curve.

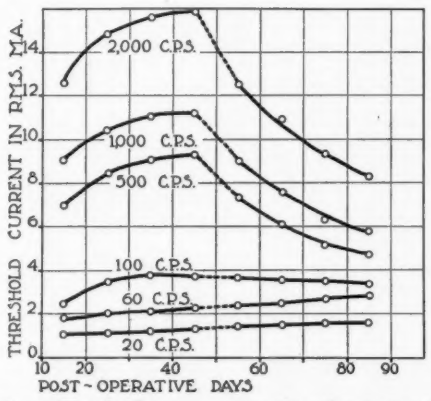

Fig. 2. Threshold current versus elapsed postoperative days in anesthetized primary suture cats. The parameter is the frequency of the stimulating current. Each point is an average of data from 5 animals.

After section of a nerve, as degeneration progresses, the threshold amperage increases at all frequencies from 20 cycles per second and more, relatively less in the case of frequencies from 20 cycles per second to 100 cycles per second, and much more for those above 100 cycles per second (Fig. 2). At a maximum of 20 milliamperes, contraction at the higher frequencies fails to appear as degeneration progresses. Thus, between 10 and 20 days after suture, only 75 per cent of the animals showed a contraction at 500 cycles per second; all at 4000 cycles per second or less. Between 20 and 30 days, 33⅓ per cent of the animals showed contraction at 5000 cycles per second; 80 per cent at 4000 cycles per second; and all at 3000 cycles per second or less. Between 30 and 40 days, none contracted at 5000 cycles per second; 66⅔ per cent at 4000 cycles per second; all at 3000, or less. Between 40 and 50 days, none contracted at 4000 cycles per second; 25 per cent at 3000 cycles per second; 66⅔ per cent at 2000 cycles per second; and all at 1000 cycles per second. Between 50 and 60 days, 50 per cent at 3000 cycles per second; all at 2000 cycles per second. Between 60 and 70 days, 25 per cent contracted at 4000 cycles per second; 75 per cent at 3000 cycles per second; all at 2000 cycles per second. Between 70 and 80 days, 60 per cent contracted at 5000 cycles per second; 80 per cent at 4000 cycles per second; and all at 3000 cycles per

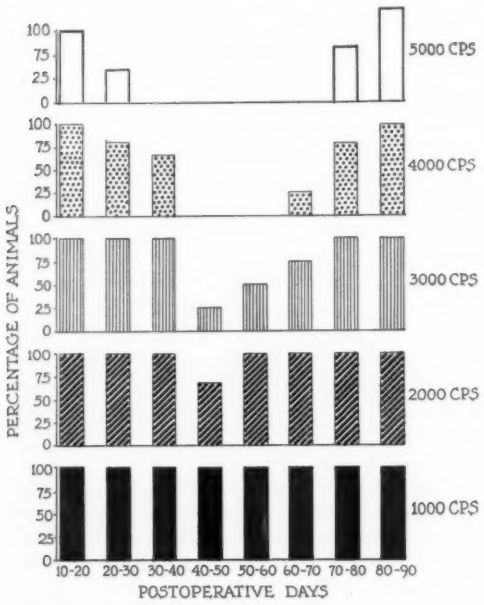

Fig. 3. Five histograms showing the percentage of animals in which contraction could be observed when using 20 milliamperes (root mean square) as the maximal value of current on various postoperative days. In each histogram, the parameter is the frequency of the stimulating current.

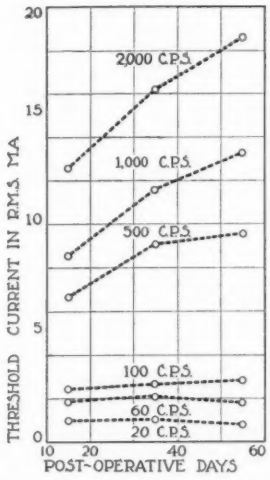

Fig. 4. Threshold current versus elapsed postoperative days in anesthetized denervated cats. The parameter is the frequency of the stimulating current. Each point is an average of data from 3 animals.

second. Between 80 and 90 days, all contracted at 5000 cycles per second (Fig. 3).

Thus as degeneration progresses, stimulation by relatively large currents fails to produce contraction at higher frequencies and as regeneration occurs and progresses, such currents again become effective at higher frequencies. However, the threshold amperage for frequencies of 100 cycles per second and more continuously diminish, but remain high as compared to the normal, even after good motor recovery is present. For frequencies of 60 cycles per second and less and particularly for very slow frequencies, one cycle or less per second, the threshold amperage increases as has been described by us in the case of the progressive current (9).

When regeneration of a severed nerve is prevented and prolonged denervation produced, the threshold amperage for higher frequencies remains high, whereas for frequencies of 60 cycles per second and particularly very slow frequencies of one or less cycles per second, the amperage diminishes still more than is seen after primary suture and is at its minimum at about the 55th day (Fig. 4).

We have already pointed out that for the normal cat muscle with the percutaneous stimuli with larger electrodes, there is no optimum frequency and no symmetry in the two branches of the curve, but rather a wide band of from 100 cycles per second to 20 cycles per second, wherein there was a very small change in amperage. At sometime between 20 cycles per second and one cycle per second the amperage rises slightly, but at one cycle in 1.33 seconds the amperage is but 1.1 milliamperes (Fig. 5).

As the muscle degenerates and before complete denervation is present, this long band disappears and there is a continuous drop of threshold amperage from, say, several hundred cycles per second to 20 cycles per second. It continues to decrease steadily and gradually to 0.75 cycle per second. It remains the same at 0.5 cycle per second, then very slowly and slightly rises; if any optimum frequency or band can be determined it is at 0.75 cycle per second (Fig. 6). This is not unexpected, since the portion of the curve representing low frequencies is probably related to

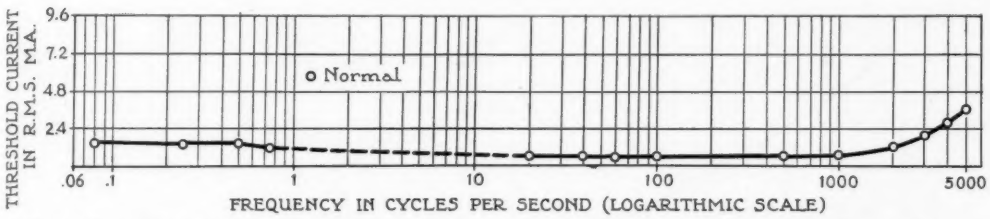

Fig. 5. Optimum frequency band in the strength frequency curve of the gastrocnemius muscle in the normal cat.

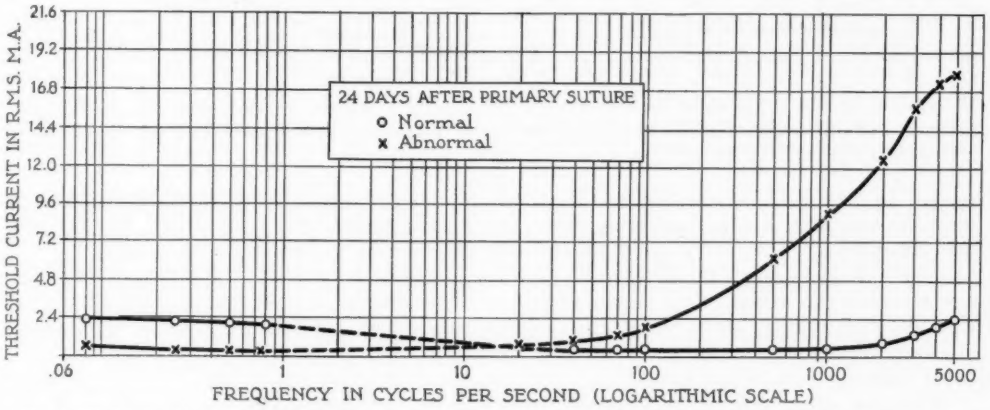

Fig. 6. Optimum frequency band in the strength frequency curve of the gastrocnemius muscle in the cat 24 days after primary suture of the sciatic nerve.

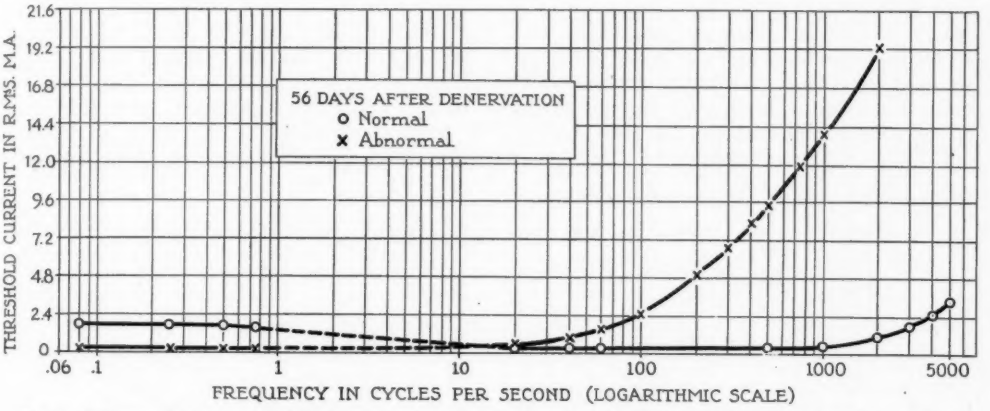

Fig. 7. Optimum frequency band in the strength frequency curve of the gastrocnemius muscle in the cat 56 days after removal of a segment of the sciatic nerve.

the alpha curve, with longer chronaxie and lower optimum frequency.

When the muscle is completely denervated, then the shift of the band of optimum frequencies can more readily be seen. There is a continuous diminution in the threshold amperage from, say 2000 cycles per second to 20 cycles per second. Then from 20 cycles per

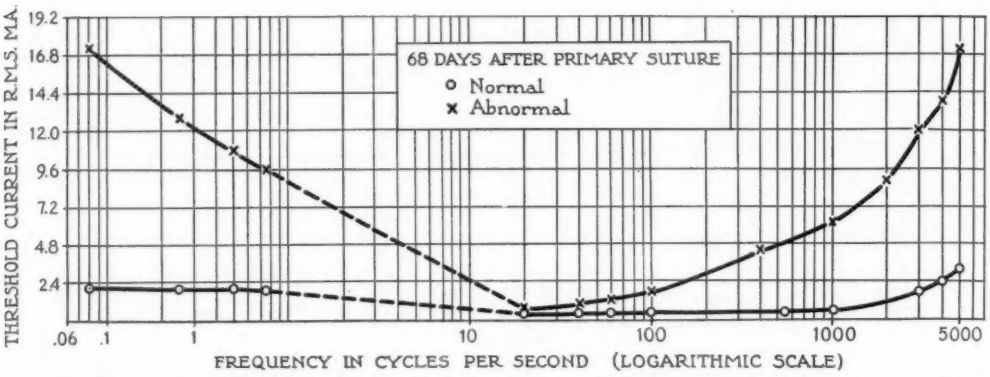

Fig. 8. Optimum frequency band in the strength frequency curve of the gastrocnemius muscle in the cat 68 days after primary suture of the sciatic nerve.

second to 0.75 cycle per second we have no data, as indicated by the connecting lines in the illustration. From 0.75 cycle per second to 0.08 cycle per second, the threshold amperage remains the same. This corresponds to Coppee's observation of the alpha curve when strength frequency curves were obtained by using large fluid electrodes (Fig. 7).

When the nerve muscle complex shows recovery, an entirely different situation is present. As in the other cases, there is a diminution of threshold amperage from 5000 cycles per second to 20 cycles per second; between 20 cycles per second and 0.75 cycle per second we have no data, but at these frequencies the amperage is quite high and steeply increases as frequency diminishes. In this case the optimum frequency would be between 20 cycles per second and 0.75 cycle per second. Although asymmetrical, there are two high branches of a skewed curve (Fig. 8).

As has been seen, the strength frequency curve in the case of the normal muscle is a continuous one. During the state of degeneration from the earliest date after section at which we have examined animals, 13 or 14 days, discontinuity in the curve can be demonstrated. Early in degeneration several, usually three, discontinuous curves may be seen. One is usually found from 20 to 100 cycles per second, another from 100 cycles per second to frequencies varying from 700 to 3000 cycles per second, and a third from 700 to 3000 cycles per second and upward (Fig. 9).

Immediately before the state of denervation, there is a tendency for the curve to show

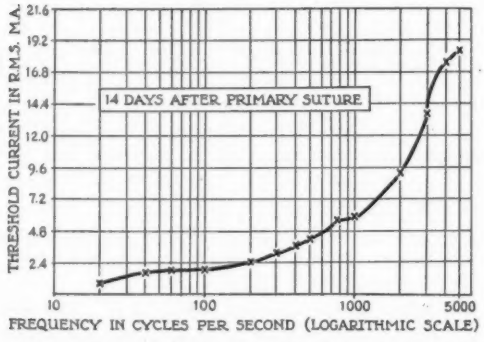

Fig. 9. Strength frequency curve of the gastrocnemius muscle in the cat showing three discontinuities, 14 days after primary suture of the sciatic nerve.

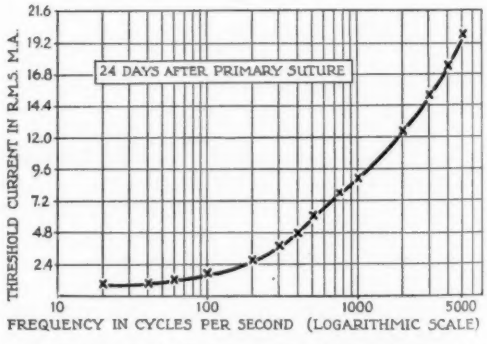

Fig. 10. Strength frequency curve of the gastrocnemius muscle in the cat showing two discontinuities, 24 days after primary suture of the sciatic nerve.

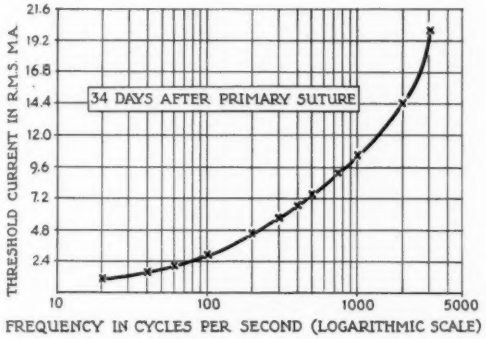

Fig. 11. Strength frequency curve of the gastrocnemius muscle in the cat showing no discontinuities, 34 days after primary suture of the sciatic nerve.

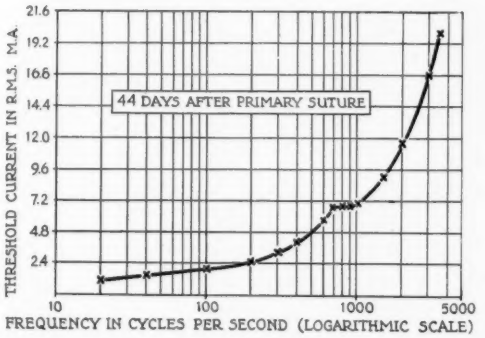

Fig. 12. Strength frequency curve of the gastrocnemius muscle in the cat showing two discontinuities, 44 days after primary suture.

but two discontinuities, the one from 100 cycles per second to slower frequencies disappearing (Fig. 10). During denervation occurring at varying days from 25 to 35 days the curve is continuous (Fig. 11).

As recovery begins at varying days, from 34 to 50, a discontinuity occurs at frequencies from 700 to 1000 cycles per second (Fig. 12); as recovery continues the acuteness of the angle between the two curves diminishes until discontinuity disappears. However, at this time for frequencies below 100 cycles per second, a discontinuity again appears and lasts for a long time after motor recovery (Fig. 13).

DISCUSSION

The characteristic changes from the normal strength frequency curve to that during degeneration are:

1. An increase of threshold amperage at all frequencies from 20 cycles per second and more, relatively less in the case of frequencies from 20 cycles per second to 100 cycles per second, and much more for those above 100 cycles per second.

2. With large constant amperage, say 20 milliamperes, there is a falling out of response of effective stimulation at higher frequencies, at first 5000, then 4000, then 3000, perhaps 2000 cycles per second.

3. The long band of optimum frequencies from 20 cycles per second to 100, or at times more, disappears and there is a continuous drop of threshold amperage to 20 cycles per second, and below that a steady but gradual decrease to 0.75 cycles per second.

4. The appearance of discontinuities in the curve, often three in number, most constantly, one from 20 to 100 cycles per second, another from 100 cycles per second to 700 to 3000 cycles per second, and a third from 700 to 3000 cycles per second and upward.

The changes during denervation are:

1. The threshold amperage for higher frequencies remains high, whereas for frequencies of 60 cycles per second and particularly very slow frequencies of one or less cycles per second, the amperage diminishes still more than is seen after primary suture and is at its minimum at about the 55th day.

2. There is a shift of the band of optimum frequencies so that there is a continuous drop in amperage from 2000 cycles per second to 20

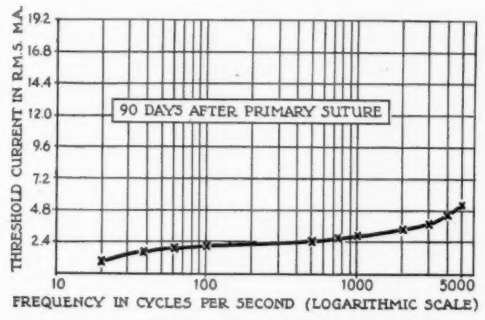

Fig. 13. Strength frequency curve of the gastrocnemius muscle in the cat showing two discontinuities, 90 days after primary suture.

cycles per second, then from 20 cycles per second to 0.75 cycle per second no data are available; however, from 0.75 cycle per second to 0.08 cycle per second the threshold amperage remains the same, indicating a band of optimum frequencies extending as low as 0.08 cycle per second.

3. The strength frequency curve is continuous.

During regeneration, there is a diminution of threshold amperage from 5000 cycles per second to 20 cycles per second. Between 20 cycles per second and 0.75 cycle per second we have no data, but at 0.75 cycle per second the amperage is quite high and increases steeply as frequency still further is diminished. In this case, although asymmetrical, there are two high branches of a skewed curve. A discontinuity reappears at frequencies of from 700 to 1000 cycles per second. The acuteness of the angle between the two curves then progressively diminishes and a continuous curve at frequencies of above 100 cycles per second results. At the same time, a discontinuity at frequencies below 100 cycles per second appears and continues long after motor recovery has occurred.

CONCLUSIONS

1. The threshold amperage at various frequencies in the normal, degenerating, denervated, and recovering state of muscles is described.

2. A shifting of the band of optimum frequency to low frequencies below one cycle per second is characteristic for degenerating and denervated muscle.

3. The appearance of two equally high branches of a skewed curve is characteristic of recovering muscle.

4. During early degeneration, at least three discontinuous curves may be recognized, later but two. During denervation the strength frequency curve is continuous. During regeneration it again becomes discontinuous.

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THE FASCIA-PATCH TRANSPLANT IN THE REPAIR OF HERNIA

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ALTHOUGH the surgical techniques devised by Bassini in 1889 and Halsted in 1890 contributed a marked advancement to the prevalent ideas of radical cure for inguinal hernias, it is a recognizable fact that the incidence of recurrence following operation is still too high; this is evidenced by the development of the many modifications of the original operations of these men to the present date. Reports from various hospitals and large clinics indicate that the rate of recurrence of all hernias varies from 1 to 10 per cent for the indirect type, and from 10 to 25 per cent for the direct type. These figures alone indicate that the problem of inguinal hernia repair is as yet not completely solved.

However, in surgical circles, there still seems to be a universal agreement that the repair of a defective abdominal wall, which Bassini and Halsted considered an essential part of their operations, is a fundamental factor in the successful repair of inguinal hernia. Consequently, in those more difficult cases in which the defect in the abdominal wall cannot be obliterated by the approximation of the internal oblique muscle and the conjoined tendon to Poupart's ligament without undue strain on the retaining sutures, other methods were devised. Among the better known techniques in such cases are the relaxing incision in the lower rectus sheath to reduce the tension on the sutures uniting Poupart's ligament to the internal oblique muscle and conjoined tendon, and the use of transplanted fascia by which the abdominal wall defect is obliterated. Transplanted fascia has been used for this purpose both as fresh autogenous, and as preserved animal grafts; it has also been employed both in the form of a patch, and in strips of interlacing sutures.

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Although McArthur in 1901 was probably the first to use fascia in the form of sutures in the repair of inguinal hernia, it was Kirschner in 1909 who made the first systematic study on the transplantation of free fascial grafts; he reported many successful free fascial transplants for various purposes and placed the method on a sound working basis. Although he did not establish the viability of transplanted fascia by his experiments, very little has been added to the practical value of his method. In the same year, 1917, that Lewis published experimental and clinical evidence showing the rehabitation of transplanted fascia, Nageotte attracted considerable attention by reporting his results in the transplantation of "dead" grafts. He successfully repaired anatomic defects in tendons of living animals by replacing the defect with pieces of tendon which had been preserved in alcohol. Experimental work by Gallie and Le Mesurier in 1924 showed that the transplanted fascia became surrounded by a delicate vascular membrane which vascularized the fascial fibers of the graft. The popularity of the use of fascia in the form of sutures in hernia repair is probably due in a large measure to the enthusiastic reports of these men. Being stimulated by the reports of Nageotte, and Gallie and Le Mesurier, Koontz later reported favorably upon the use of preserved ox fascia used both as a patch and in strips as sutures. However, Horsley's work in 1931 led him to the conclusion that preserved fascia is inferior to fresh autogenous fascia when transplanted.

When the treatment of hernia by means of transplantation of fascia lata patches first came into prominence, it was believed for a time that the difficulties of a radical cure for hernia had been overcome; but with the revival of the use of fascia transplants in the form of strips as suture material by Gallie and Le Mesurier in 1921, the popularity of the

Fig. 1. A larger direct inguinal hernia successfully treated by the fascia patch method. This hernia was of several years' duration with progressive increase in size in a middle aged negro. At time of operation a large nonhealing ulcer was present on lower posterior aspect of scrotum. No previous hernia repairs had been attempted.

Fig. 2. Large indirect inguinal hernia of 6 years' duration in a 65 year old white male successfully repaired by fascia patch method. Previous Bassini type of repair had failed. Ulceration on the left lower aspect of the scrotum showed malignant changes and the area was excised at time of operation.

fascia patch method diminished. However, members of the surgical staff of the John Sealy Hospital have used this method over a period of years, and a review of the results leads us to the belief that the procedure should have a definite place in the surgeon's armamentarium.

In a 28 year period, beginning in 1916 and ending in 1944, we have used the fascial patch transplant method in 175 patients who presented themselves for cure of hernia. A breakdown of this group showed that of the 175 cases operated upon, 93 patients had the direct type of hernia on which 65 previous hernia repairs had been attempted but failed. Forty patients with the indirect type of hernia reported 12 previous operations with recurrence, and 42 patients with various forms of ventral and incisional types of hernia reported 30 previous surgical procedures terminating in failure. As was expected, this analysis indicates that the ventral and direct types of hernia offer the greater problem in obtaining a permanent cure (Figs. 1 and 2). The fascial patch method was used only in severe cases in which it was obvious that the usual types of hernia repair would terminate in failure; this is evident by the fact that these 175 patients had had 108 previous operations which had failed. We have not used the patch in ventral hernia when it has been possible to bring the muscle and fascia margin of the hernial ring together. Some of these have been very large, and the most severe tests of all hernias are in the postoperative ventral type with any procedure.

Since our patients reside over the entire State of Texas we have been able to obtain reliable, periodical, postoperative examinations in only 129 of these 175 patients. This group of 129 patients with hernias had had 80 previous repairs which failed. Postoperative

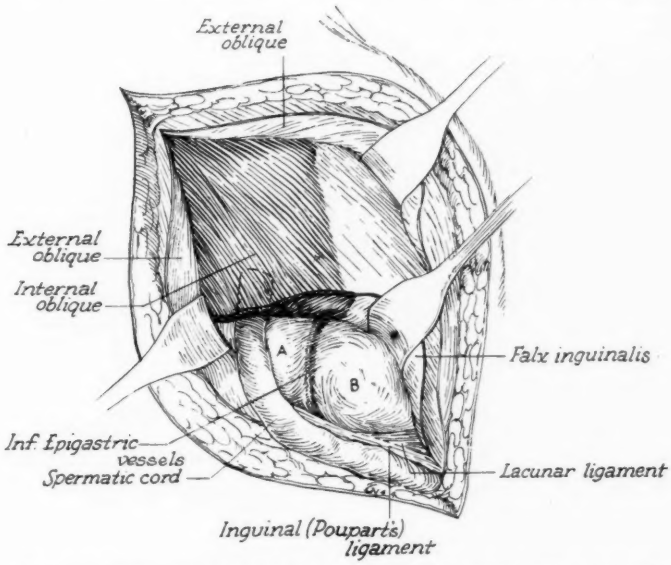

Fig. 3. A diagrammatic sketch of a dissection of the inguinal region, indicating the various structures which must be neatly dissected and accurately identified before the successful implantation of a fascia patch for hernia repair can be anticipated. *A*, Area of origin of the sac in an indirect hernia as it leaves the abdominal cavity through the internal abdominal ring and enters the inguinal canal with the spermatic cord; *B*, area of Hesselbach's triangle through which the sac of a direct hernia protrudes and passes through the abdominal wall at the external abdominal ring.

follow-ups of this group of patients who were treated by the fascia-patch transplant method, revealed failure and recurrence of the hernia in 14 cases. We believe that the unfollowed cases would show few recurrences, since these patients would probably have returned for treatment had further trouble resulted (Table I). An analysis of this group of 129 cases reveals that the greatest incidence of failure by the use of the fascial patch transplant is in the ventral type of hernia, and the lowest incidence is in the indirect type. In 30 cases of indirect hernia, reporting 10 previous operations which failed, there was 1 recurrence, while 33 patients with 29 previous operations for ventral hernia had 6 failures by the fascial patch transplant method. Also, 7 failures of the method were found in 66 patients with direct hernias who reported 41 previous operations.

In the 14 cases in which the method failed, the recurrence was apparent within 6 months in the majority of cases, and with one exception, which was discovered after 18 months, all failures were apparent within 1 year after operation. All the other cases reported as

TABLE I.—HERNIA REPAIR BY FASCIA PATCH TRANSPLANT

129 Operated Cases: 1916–1944 with Follow-ups

Type	No. of cases	Previous operations with recurrence		Fascia patch method with recurrence	
		No.	Per cent	No.	Per cent
Indirect hernia	30	10	33.33	1	3.33
Direct hernia	66	41	62.12	7	10.60
Ventral and incisional herniae	33	29	87.87	6	18.18
Total	129	80	62.01	14	10.85

Table I. An analysis of the series of 129 hernia cases treated by the fascia patch method according to the type of hernia, indicating the number and percentage of failures by the fascia patch method as well as that of all other previous and various types of repair which failed, before the fascia patch method was used in each group.

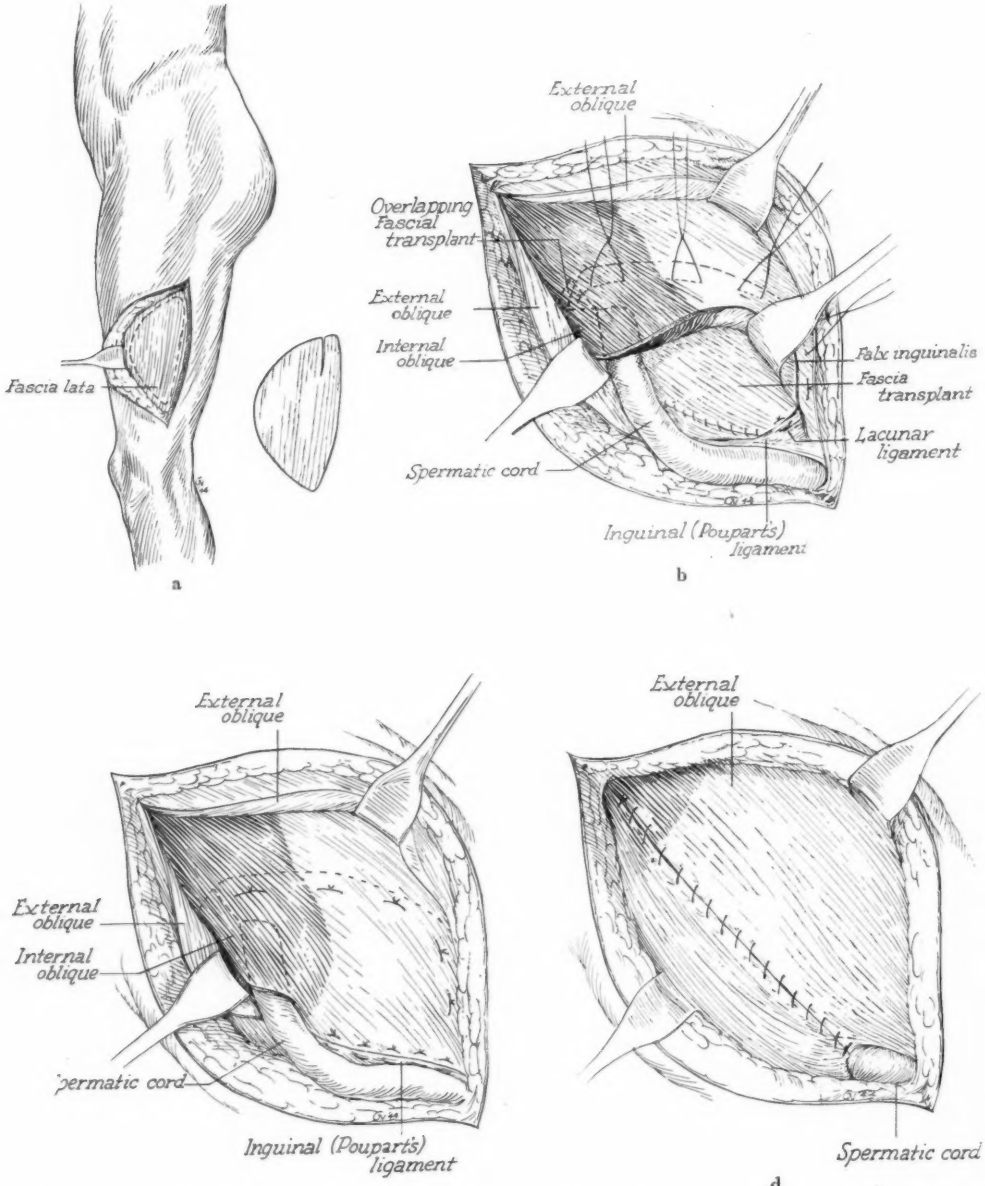

Fig. 4: a, Fascia patch excised from the thigh and notched for repair of inguinal hernia. b, Fascia transplant in place, firmly sutured to the lacunar and Poupart's ligaments before its upper edge is anchored high up under the conjoined tendon, and internal oblique and transversus muscles. c, Edge of internal oblique muscle and conjoined tendon buttressed to Poupart's ligament over the fascia patch but below spermatic cord. d, External oblique aponeurosis sutured to Poupart's ligament over spermatic cord down to superior crus of external abdominal ring.

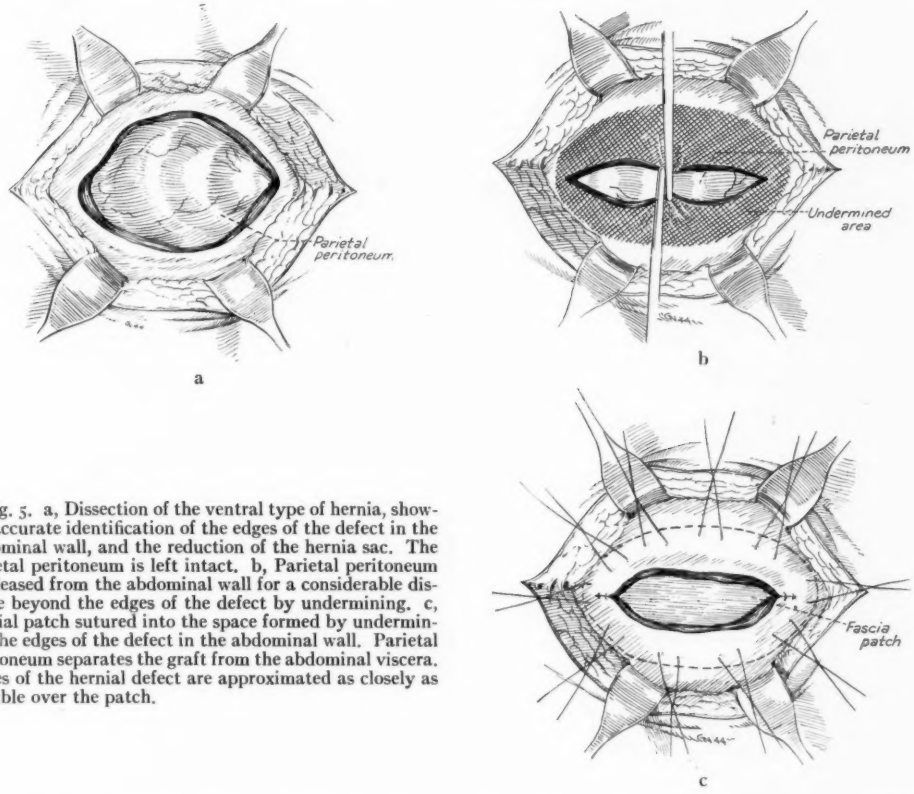

Fig. 5. a, Dissection of the ventral type of hernia, showing accurate identification of the edges of the defect in the abdominal wall, and the reduction of the hernia sac. The parietal peritoneum is left intact. b, Parietal peritoneum is released from the abdominal wall for a considerable distance beyond the edges of the defect by undermining. c, Fascial patch sutured into the space formed by undermining the edges of the defect in the abdominal wall. Parietal peritoneum separates the graft from the abdominal viscera. Edges of the hernial defect are approximated as closely as possible over the patch.

failures of the method were anticipated due to such complications as severe wound infections and the development of a sudden gastric hemorrhage followed by anemia and ascites during convalescence. In 2 other failures, difficulty was encountered during the operation in obtaining firm tissues on to which to suture the fascial patch transplant, the patients becoming extremely obese and having flabby musculature.

The analysis of this series of cases leads us to believe that the use of the fascial patch transplant in the radical cure of hernia is a procedure that deserves more merit than is usually accorded this method. This is especially true when it is borne in mind that all cases in this series were severe in nature, and that the operative procedure was carried out by 13 different surgeons, the majority of whom were still in the process of acquiring their graduate surgical training. We are impressed by the results obtained by the fascial suture method as advocated by Gallie and Le Mesurier, but the proper use of the fascial patch transplant is an anatomical procedure in that it is a replacement of deficient tissue in the defect of the abdominal wall. In comparison with the fascia suture method the operation is relatively easier, is of shorter duration, requires less handling of tissues, and causes no distortion of surrounding tissues. If the principles of technique and wound-healing are borne in mind when the operation is performed, the fascial patch transplant method should enjoy greater success than has been universally accorded it in the past.

The technique of the patch method of fascial grafts for inguinal hernia repair as used

Fig. 6.

Fig. 7.

Fig. 8.

Fig. 6. An indirect inguinal hernia of long standing in middle aged white male successfully repaired by fascia patch transplant. Abdominal rings and inguinal canal were markedly dilated.

Fig. 7. Same patient as shown in Fig. 6, 1 month after operation. Note bulge on lateral surface of left thigh where fascia was removed for hernia repair.

Fig. 8. Same case as shown in Figs. 6 and 7, showing herniation of muscles of the thigh in area where fascia lata was excised 1 month previously.

by us is not complicated but is relatively simple. We have used it as described here since 1916 and have found no alterations in the procedure necessary since that time. The type of anesthetic used makes very little difference, if any, as regards the success of the operation itself, provided the vomiting, retching, coughing, and straining which frequently follow the use of a general anesthetic can be eliminated or kept at a minimum. For this reason in a great majority of the cases reported in this series the operation was carried out under local anesthesia. The skin is infiltrated with 0.25 per cent novocain with epinephrine just along the line of incision above Poupart's ligament; the skin and Scarpa's fascia are incised, and bleeding points are clamped. About 20 cubic centimeters of the novocain solution is then injected just beneath the aponeurosis of the external oblique muscle above the area of the internal abdominal ring. This infiltration completely blocks the ilio-inguinal and iliohypogastric nerves before they are exposed. During the few minutes it takes for this injection to complete the anesthesia, the bleeding points of the subcutaneous tissue are ligated. The aponeurosis of the external oblique muscle is then split in the direction of its fibers in such a manner that the line separation of these fibers passes through the height of the superior crus of the external abdominal ring. By retracting the opposing edges of the split aponeurosis the spermatic cord and hernial sac are exposed. The hernial sac is opened, separated from the spermatic cord structures and the ilio-inguinal and iliohypogastric nerves, and is cut accross after being ligated at the internal abdominal ring. The conjoined tendon, the internal oblique muscle, transversalis fascia, and Poupart's ligament are exposed as in the usual hernia operation. It is at this point one must decide whether or not it will be necessary to use a fascial transplant. If it is to be used, a piece of fascia lata is excised from the lower or middle one-third of the lateral side of the thigh (Fig. 4, a). Here the fascia lata has no posterior attachments to the underlying muscles and is more easily obtained than in the upper thigh. The size and shape of the "patch" excised from the fascia lata must vary with the dimensions and configuration of the defect to

be repaired. It must be borne in mind that the patch must be larger than the defect to allow overlapping of its edges, for the strength of the repair depends both on the type, and the amount of union by fibrosis between the graft and the overlapping edges of the defect. A notch is cut in one end of the fascial transplant to receive and fit snugly around the spermatic cord where it leaves the abdomen. Before the graft is put to place one must make sure that all loose areolar and fatty tissues have been removed from the graft and the structures to which it is to be sutured, to insure a firm union between the graft and the edges of the defect (Figs. 4 a, b, c, and d). The graft is transferred to the inguinal wound with its upper edge placed beneath the muscle and stitched with mattress stitches to the under surface of the internal abdominal oblique and transversus muscles. The lower edge is secured to the shelving portion of Poupart's ligament either by several mattress sutures or by a continuous suture, obtaining as much surface contact between these two structures as possible. The spermatic cord is brought out through the notch in the graft at the point where it leaves the abdomen. The mattress sutures through the internal oblique muscle and conjoined tendon are not tied until the inferior edge of the graft has been firmly attached to Poupart's and the lacunar ligaments. The internal oblique muscle edge and conjoined tendon are then buttressed to Poupart's ligament, as in the Bassini operation, and the external oblique is sutured to Poupart's ligament in the same way. The repair of the direct or indirect hernia by this method is practically the same, since the areas reinforced by the fascia-patch graft covers both Hesselbach's triangle and the edges of the internal abdominal ring. It is especially important in repairing the direct hernia that the corner of the fascia patch be securely sutured and anchored not only to the shelving portion of Poupart's ligament but also to the lacunar ligament. In the indirect hernia special attention is called to the fact that the notch cut in the fascia patch to receive the spermatic cord should be sutured snugly around the cord but not so tightly as to interfere with circulation through the spermatic cord.

The repair of a ventral hernia by the fascial patch method is similar to the technique used in repairing an inguinal hernia. The patch must be cut of such configuration and size as to allow considerable overlap of the surrounding tissues of the defect to insure enough area of contact between the two in order that a union may be obtained strong enough to withstand the physiologic stress and strain. The graft is sutured to place below and beyond the muscular edges of the defect in the abdominal wall by mattress sutures (Figs. 5 a, b, c). When possible the edges of the defect are imbricated or approximated over the transplant, the line of suturing running parallel to the fibers of the surrounding tissues and of the graft. Although the graft is placed below the muscular edges of the defect, the peritoneum or omentum should intervene between the graft and the abdominal viscera to prevent the formation of dangerous adhesions which may terminate in intestinal obstruction.

We have also used the fascia patch in 2 cases of diaphragmatic hernia, not included in this series, with good results. The intrathoracic approach was used, the fascial patch was sutured over the defect to the superior surface of the diaphragm in an overlapping manner. The success of the procedure was verified by subsequent x-ray studies as well as by the remission of symptoms. One of these patients died 2 years after the operation from other causes, and at autopsy the diaphragm was found to be intact, the fascial patch being firmly adherent to the bed to which it was sutured. There were also firm adhesions between the superior surface of the graft and the visceral pleura of the lung on one side, and between its inferior surface and the gastric serosa on the other.

OBSERVATIONS

The majority of failures previously reported are probably due to errors in technique and possible disregard for certain fundamental principles of wound healing. Gallie and Le Mesurier, as well as Koontz and Haas have shown clearly by their investigations that the union between muscle, aponeuroses, and tendon is by the formation of scar tissue, and that there is no proliferation of the essential cells of such tissues. Scar tissue differs from

fascia in that, although it is composed of similar white fibers, these fibers are loosely arranged and irregular, and, when subjected to constant strain, show a tendency to stretch. This fact indicates that the firmness of union between the graft and surrounding tissues is directly proportional to area of contact and union between the graft and the structures to which it is sutured (Fig. 6). The strength of the union depends on the care with which areolar tissue has been removed and prevented from intervening between the graft and its attachments to muscle or ligaments. Union which is produced by newly formed connective tissue will range from the loose texture of areolar tissue to the firmness of ordinary scar. Actual scraping and scarification of the contacting surfaces of the graft will produce firm scar. Koontz also obtained a firmer union by cutting away the surface of the muscle to be sutured to the fascia. This was verified by the experimental work of Haas which showed that in the union of muscle to fascia, the perimysium, endomysium, and the variable cellular elements of the transplanted fascia play the major rôle. In the 6 patients of our series whom we have reoperated upon we have found that there was no absorption of the graft, but that failure was due to either inclusion of areolar tissue in the plane of union between the graft and conjoined tendon with consequent excessive stretching, or insufficient area of actual contact between the graft and its bed to obtain a union strong enough to withstand the normal physiological strain. In such cases in which mechanical difficulties prevent placing the graft in actual contact with surrounding tissues over a sufficient distance to obtain enough scar tissue union to withstand the physiological strain, the fascial patch method is not indicated, and the fascial suture should be used, as the strength of the union here depends on the suture itself and the tissues into which it is laced (Fig. 7).

Gratz points out that failure of many fascial patch transplants was due to the disregard of the physiological principles of stress and strain. A combination of shearing and tensile stress may result in the disintegration of the transplant, unless it is cut parallel to its fibers, and placed in its bed so that its fibers run parallel to those of Poupart's ligament, or those of the rectus sheath when used in ventral hernias.

The blood supply to the fascial transplant is not an important factor, as the viability of the graft is dependent on the seepage of lymph through its spaces. However, to insure adequate lymph supply to the graft, it again becomes important to remove adequately all coverings of loose areolar and fatty tissues from the graft before it is sutured into place.

Koontz and Hertzler advocated the tying of sutures and ligatures tightly when the transplant is being fixed to the surrounding tissue. This not only insures close contact of the graft to its attaching structures, but also produces fibrin formation by traumatizing the muscle, and leads to fibrosis upon which depends the union. Tight ligatures will cause no necrosis because of the rich blood supply in muscle.

In many of our cases bulging has occurred at the site from which the transplant was taken from the fascia lata. In most of these cases no unfavorable symptoms occurred except the noticeable herniations of the vastus lateralis muscle (Fig. 9). In time these deformities gradually disappear, possibly due to the contracture of a layer of scar tissue which forms in that area. Foshee, in a recent study, concluded that there is a regeneration of the excised fascia lata. In several cases in which we have again operated upon the thigh for purposes of obtaining additional amounts of fascia lata for various reasons, we have found conditions, both grossly and microscopically, identical to those described by Foshee. Since we have never observed the redevelopment of the strong middle layer of fibers which run in a vertical direction, but have only found the reformation of the thinner and weaker outer and inner layers of the fascia lata, we are not inclined to consider this phenomenon as a true regeneration of the fascia lata, but rather the formation of a layer of scar tissue in which the direction of its fibers is influenced to a great extent by the forces of stress and strain from the underlying active muscles of the thigh. Certain members of our group have overcome this difficulty of early bulging of the thigh by obtaining the fascial transplant

from the posterior border of the fascia lata just above the midpoint of the thigh. At this level the underlying vastus lateralis muscle is covered by an aponeurosis from which its muscle fibers arise. Herniation is prevented by the suturing of the cut edge of the fascia lata to the aponeurotic origin of the vastus lateralis. Since no unfavorable symptoms have been produced by the herniation of the thigh muscles through the donor site of the fascia lata patch, this procedure may be considered as of minor importance.

In our group of cases various types of suture material have been used, namely: silk, linen, cotton, and chiefly chromic catgut, without any appreciable differences in the end-result of the operation.

CONCLUSION

We believe that the use of the patch type of free fascial transplant in the surgical cure of difficult and large hernias is of definite value in selected cases, and that proper observance of certain principles of technique and wound healing in its use will result in a greater degree of success than the method has enjoyed in the past.

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TOTAL PANCREATECTOMY, TOTAL GASTRECTOMY, TOTAL DUODENECTOMY, SPLENECTOMY, LEFT ADRENALECTOMY AND OMENTECTOMY IN A DIABETIC PATIENT, RECOVERY

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THE surgery of pancreatic tumors has become well established as a result of experiences in recent years. It is not only possible to resect large portions of this organ but its total extirpation can now be envisaged. The purpose of this report is to record an instance of very radical attack upon cancer of the body of the pancreas that had extended on to the stomach, into the left adrenal gland, and had metastasized to the omentum and glands of the lesser curvature of the stomach. The patient's history is also of interest because he was diabetic before operation. The diabetes was not due to destruction of pancreas by tumor.

F. W. (328218), white, male, 53 years of age, was admitted to the medical service of one of us (H.T.R.) February 24, 1944, because of watery, foamy stools, several to as high as 20 a day, for the previous 2 years. There was some abdominal pain at first but this did not continue. There was loss of 50 pounds in weight during this period, yet his appetite remained "ravenous." A complete examination was carried out. The blood was normal. The presence of rather typical steatorrhea was confirmed. He was found to be rather severely diabetic and required 60 to 90 units of insulin daily with carbohydrate intake of 400 to 900 grams and total caloric value of daily diet varying from 2500 to 5500 calories. Roentgenographic examinations of stomach, duodenum, chest, and colon were negative. In surgical consultation (A.B.) it was believed that laparotomy was not indicated as he was improving on medical management and was having no pain.

He was discharged from the medical service May 14, 1944. There was no pain, he had gained *37 pounds in weight.* Pancreatin seemed to have had no effect upon the number and quality of the stools. The latter at first contained much fat but later this was reduced by decreased dietary fat; they continued to be soft.

He was readmitted August 24, 1944, because of moderately severe icterus of 3 weeks' duration; pruritus, 1 month; abdominal pain in right upper quadrant, at times very severe, 1 month. Improvement in diarrhea was noted in that during the first week in the hospital he had only two stools a day. Direct van den Bergh 5.6 milligrams per cent; indirect, 7.5 milligrams per cent. Examination of the abdomen was negative except for moderate smooth enlargement of the liver. The gall bladder was not palpable.

Exploratory laparotomy was now thought to be indicated and was performed September 7, 1944, as follows (Fig. 1):

1. The abdomen was entered through a high midline incision. It was immediately apparent that the contracted greater omentum, although not adherent to surrounding structures, contained numerous spherical metastatic nodes. Before anything further was undertaken, the entire redundant portion of omentum was resected by incision along the attachments to transverse colon. The gall bladder appeared normal and contained no stones. It was not distended. The common duct was slightly enlarged.

2. Exploration revealed no gravitational metastases in the pelvis, nor on the peritoneum, and there were no metastatic nodules in the liver. The stomach appeared to be bound down by adhesions on its posterior wall. The gastrocolic omentum was divided and the transverse colon was retracted downward; it now became evident that the primary growth was in the body and tail of the pancreas, that there was direct extension into posterior gastric wall and especially into the nodes along the lesser curvature. The latter formed a dense, matted mass almost to the esophagus.

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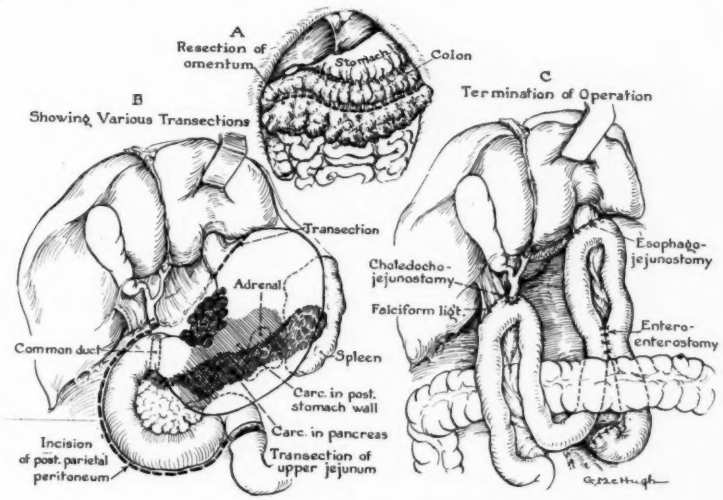

Fig. 1. Various steps in operative procedure.

The duodenum and head of the pancreas were mobilized by incision of peritoneum along the greater curvature of the duodenum.

The ligament of Treitz was transected and the duodenojejunal junction was mobilized. The superior mesenteric vein was exposed below its emergence from beneath the neck of the pancreas. The duodenojejunal junction was transected with invagination of the distal stump.

4. The right and left gastric vessels were divided and ligated. The head of the pancreas and duodenum were further mobilized and elevated. By sharp dissection the neck of the pancreas was elevated from the superior mesenteric vessels. The duodenum and the head of the pancreas were retracted downward and the common duct was transected at the level of the upper border of the first segment of the duodenum; below this level it was apparent that the common duct was infiltrated and constricted by neoplastic extension from the pancreas. The duodenum, head of pancreas, and lower stomach were now fully mobilized.

5. The right hand was passed over the diaphragmatic aspect of the spleen, and the splenodiaphragmatic ligament was divided. The spleen was brought downward and mesially to mobilize the tail of the pancreas and the greater curvature of the stomach. The splenocolic ligament was divided.

6. Dissection to elevate the entire body of pancreas *en masse* with the stomach was begun just to the left of the level of the superior mesenteric vessels since the head of the pancreas and duodenum had been mobilized up to that point. In dissecting free the body of the pancreas, the latter fragmented and seemed to be completely replaced in its central portion by tumor, which was also densely adherent to posterior upper retroperitoneal tissues. All gross evidence of tumor and pancreas was elevated. The spleen was elevated and this brought up the tail of the pancreas. As the involved mid portion of body of the pancreas was being mobilized, it became apparent that the left adrenal gland which was adherent to it because of tumor infiltration was also being mobilized for excision.

7. The entire stomach, entire pancreas, entire duodenum, left adrenal, and spleen were now elevated over the left costal arch. The first long loop of jejunum was brought up through a hiatus in the transverse mesocolon to the posterior aspect of the cardiac end of the stomach and attached to it by interrupted silk sutures. The stomach and other structures were then cut away; the level of transection being about 1½ centimeters below the

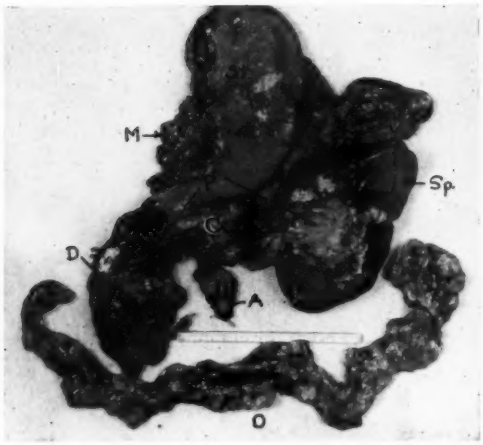

Fig. 2. Surgical specimen consisting of *St*, practically the entire stomach; *D*, entire duodenum; *P*, entire pancreas with, *C*, carcinoma arising in body and tail; *A*, left adrenal gland; *Sp*, spleen; *O*, entire retracted omentum, riddled with tumor metastases; *M*, metastases along lesser curvature of stomach.

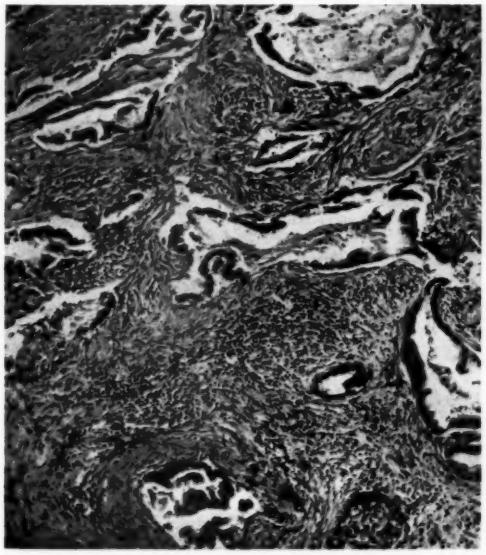

Fig. 3. Photomicrograph of section from carcinoma of the body of the pancreas. ×6.

esophagogastric junction. Anastomosis between jejunum and esophagus, that had attached a narrow cuff of gastric wall about 1½ centimeters in width, was then carried out with two rows of interrupted sutures. An enteroenterostomy was performed between afferent and efferent jejunal loops below level of transverse mesocolon.

8. The second long loop of jejunum was brought upward anterior to transverse colon and choledochojejunostomy was performed, two rows of interrupted silk sutures being used. Interrupted sutures were then placed between the jejunum distal to the latter anastomosis and the falciform ligament, to support this anastomosis.

9. The abdomen was closed with Pezzer catheter drain in left upper quadrant and large gauze pack inserted within a sheet of perforated "silkoid" to serve as a Mikulicz type drain. At the close of the operation there was no macroscopic evidence of carcinoma remaining in the abdomen.

The duration of operation was 5 hours 43 minutes. Infusions during operation consisted: 2800 cubic centimeters blood, 3000 cubic centimeters saline, 800 cubic centimeters gelatin. Blood pressure at onset of operation was, 120/70; at close of operation: 110/65. There was no "shock" at any time.

The surgical specimen is illustrated in Figure 2 and the total weight was 856 grams. It consisted of practically the entire stomach, duodenum, pancreas, spleen, omentum, and left adrenal gland. The midportion of the body of the pancreas and the tail were replaced by carcinoma. The gross appearance of the proximal portion of the body of the pancreas, the neck and head, was normal except for an extension of tumor along the superior margins to infiltrate and constrict the lower portion of common duct behind the first segment of duodenum. Histologic study revealed a typical duct cell carcinoma of the pancreas (Fig. 3). Study of the uninvolved pancreas revealed typical degenerative changes in the islets characteristic of diabetes (G. Gomori).

The postoperative course was remarkably smooth. Nothing was received by mouth for 8 days; casein digest and glucose were given intravenously for nutrition. The data concerned with parenteral fluid administration during the first 8 days postoperative are shown in Table I. Food by mouth was then gradually increased until he received a full diet by the end of 3 weeks.

Two and one-half months after operation the patient clinically was in fair condition. He was ambulatory and could have been previously discharged from the hospital but was retained for metabolic studies. The weight was stabilized at 55 to 57 kilograms. The diarrhea persisted despite administration of pancreatin. Examination of the abdomen (2½ months after operation) revealed metastatic nodules in the abdominal wall beneath the umbilicus and in the left paraumbilical region. There was

TABLE I.—INTRAVENOUS FLUIDS, BLOOD SUGARS, ETC., DURING FIRST 8 DAYS AFTER TOTAL PANCREATECTOMY AND TOTAL GASTRECTOMY

Day post-operative	5% Amigen 5% glucose c.c.	8% Gelatin in saline c.c.	5% Glucose c.c.	Saline c.c.	Blood c.c.	Plasma c.c.	Urine Vol. c.c.	Glucose in urine gm.*	Insulin amounts Prot.	Insulin amounts Reg.	Blood sugars mgm.% 6 a.m.	Blood sugars mgm.% 12 M.	Blood sugars mgm.% 6 p.m.	Blood sugars mgm.% 12 M.
Day of operation	0	800	1000	3000	2800	0	955		30		153	106		
2	800		2000			800	1850	21	30		94	440	345	381
3	1000		1000	1000 (and 5% glucose)			2550	31.9	20	35	367	401	303	281
4	2000		500	500 (and 5% glucose)	600		1350	10.2	30	70	293	255	220	124
5	2000			1000 (and 5% glucose)			1650	11.8	30	10	54	80	138	186
6	2000		500	500 (and 5% glucose)			1610	18.3	30	25	256	272	303	189
7	2000		500	500 (and 5% glucose)	600		1460	6.4	30	30	266	203	198	160
8	2000			1000 (and 5% glucose)			1400	7.8	30	30	174	188	171	138

*There was no acetone or diacetic acid at any time.

no evidence of ascites, the liver was not palpable, and the icterus present before operation had cleared completely. He ingested a 2500 caloric diet daily which included 400 grams of carbohydrates.

The patient died 3½ months after operation. Necropsy revealed abdominal carcinomatosis. No pancreatic tissue was discovered anywhere.

This is the first patient reported with fairly severe diabetes not due to tumor destruction of the pancreas, but of spontaneous origin, who has been subjected to total pancreatectomy (and total gastrectomy). Following the immediate effects of operation, the diabetes was at no time augmented in severity; on the contrary, there were periods when it appeared less severe than before total pancreatectomy. With the caloric intake equivalent to about 2500 (400 gms. carbohydrate), the insulin requirements were 30 units protamine and 10 units regular, daily. These observations raise many fundamental questions concerning the nature of diabetes mellitus in man and the exact status of the pancreas in this condition. Detailed data on the various observations made upon the metabolism of this patient following the immediate postoperative period will be published subsequently in greater detail elsewhere. Some data are presented in Table II.

Including the case here reported, 5 total pancreatectomies have been performed in this institution for carcinoma. Three of these have been previously commented upon by Goldner and Clark. Although their survival was brief, suggestive evidence of relatively moderate insulin requirements in nondiabetic patients following total pancreatectomy was presented. In Fallis' case, briefly reported by McClure, the insulin requirement in the previously nondiabetic patient after total pancreatectomy was only 26 units a day, 4 months after operation. The objectives attained in the case here reported were (a) relief from

TABLE II.—LABORATORY DATA—2½ MONTHS AFTER OPERATION

Blood	
Red blood cells	4,250,000
Leucocytes	9,700
	(no recent transfusions)
Plasma proteins, mgm. %	6.64
Nonprotein nitrogen, mgm. %	19.
Serum lipids, mgm. %	977.
Bromsulfaleine test—2 mgm. per kgm. 0% retention in 30 minutes	
Icteric index	8.
Blood amylase:	
5 months before operation—units	81.
1 week after operation—units	9.
2 weeks after operation—units	10.
8 weeks after operation—units	71.

jaundice, and (b) resection of all gross evidence of neoplasm within the abdomen *at the time of operation*. The experiences in this patient are recorded again to demonstrate the feasibility of very radical resections for abdominal cancer in encouragement of the extension of radical surgery in the treatment of malignant neoplasms.

SUMMARY

A diabetic patient with carcinoma of the body of the pancreas that had extended to adjacent viscera, successfully underwent total pancreatectomy, total gastrectomy, splenectomy, total duodenectomy, and left adrenalectomy. The diabetes was not aggravated following the operation; there were periods when, under the conditions of observation, the diabetes appeared to be less severe than before operation.

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PANTOPAQUE MYELOGRAPHY AS AN AID IN THE PREOPERATIVE DIAGNOSIS OF PROTRUDED INTERVERTEBRAL DISCS

A Preliminary Report

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THE following report is made to emphasize the fact that if the usual unilateral exploration is carried out for protruded intervertebral lumbar disc, without preoperative myelographic studies, bilateral (1, 3) or multiple (2) protruded discs as well as certain other intradural pathological lesions (8) may be overlooked.

Myelography has been largely abandoned by some surgeons in the diagnosis of herniated disc. This has been done on the basis that clinical diagnosis is sufficiently accurate and also because the older contrast media were deemed unsatisfactory. The objections to the use of air (or oxygen) have been that it frequently fails to show the presence of a small disc protrusion and that severe headache may temporarily follow its use. Lipiodol was used with caution because it could not be easily removed from the subarachnoid space and if left *in situ* might give rise to intradural irritative phenomena. Thorium dioxide solution (thorotrast) is radioactive and an irritant.

The new contrast medium, pantopaque (ethyl iodophenylundecylate) (6, 10, 11) has now made myelography a simpler and more justifiable procedure than it was in the past. Spurling and Thompson, who have been using this method routinely in all suspected discs, report very accurate interpretations. They point out that the exact level of the lesion may be localized and operation limited to exploration at the precise interspace. This seems preferable to operative exposure at two levels, which is sometimes necessary before the protruded disc is found. In addition it may be recalled that Camp reported: "12 per cent of protruded intervertebral discs in my experience have been multiple" (2).

No untoward reactions are to be expected from the use of pantopaque if the agent is removed immediately following the examination. Removal can almost always be accomplished with ease by aspiration through a 20 gauge needle as described by Kubik and Hampton. If for any reason the agent is not removed it does not give rise to any greater reaction than does lipiodol, and in time is apparently largely, if not wholly, absorbed.

In the present study 36 pantopaque myelograms were done on patients with symptoms simulating those seen in the presence of a unilateral herniated nucleus pulposus. Pathognomonic signs and symptoms were not present, however, in all cases. In the roentgenoscopic and roentgenographic examination a filling defect in the pantopaque shadow typical of a herniated disc was demonstrated in 20 cases and in 14 of these the diagnosis was verified by one of us (F. A. E.) at operation. The other 6 individuals were not explored as their condition existed prior to induction into the Army. Fourteen patients had negative myelograms. In this small series it is interesting that 2 patients had large bilateral filling defects and 2 others had evidence of diffuse intradural pathology considered to be probably arachnoiditis.

Of the 2 patients in whom myelography showed bilateral filling defects in the lumbar region, one was explored (Fig. 1), and an unusually large protruded disc was removed from the fourth interspace on the left and also a large one from the fifth interspace on the opposite side. At each level the nerve root was

Fig. 1.

Fig. 2, a.

Fig. 2, b.

Fig. 1. Two large filling defects in the column of pantopaque are evident, one at the fourth lumbar interspace on the left side and the other at the lumbosacral junction on the right as indicated by the arrows. At operation two herniated discs were removed, one from the site of each filling defect. Clinically, this patient presented signs and symptoms of a protruded disc only on the left side.

Fig. 2. a, Here is seen a bilateral filling defect at the fourth lumbar interspace probably due to herniation of a disc or hypertrophy of the ligamentum flavum on both sides. Despite the bilateral nature of the pathology, the patients' symptoms suggested only a unilateral lesion. b, The pantopaque has been removed except for one droplet in the cul-de-sac.

markedly compressed. It is noteworthy that before operation the patient had symptoms suggesting a herniated nucleus pulposus only on the left. His pain had always been referred from the lumbar region to the left leg. The ankle jerks were present, but the left was less active than the right. In this case a clinical diagnosis of protruded lumbar disc on the left was made. With such a diagnosis it seems obvious that without the aid of myelography the usual unilateral exploration would have been carried out and the herniated nucleus pulposus removed only from the fourth interspace on the left. A similar pathological lesion present at the lower level on the right would have been overlooked and recurrence of symptoms on this side would have been very likely. The other individual in whom a bilateral filling defect was present likewise had symptoms suggesting a herniated disc only on the left. Following an injury to his back in 1940 he had complained of low back pain with sciatic radiation to an area just above the left popliteal space. This had occurred in increasingly severe attacks. Anterior flexion of the lumbosacral spine was limited. The pain was aggravated both by coughing and anterior flexion of the spine. Straight leg raising was strongly positive on the left at 40 degrees and the left ankle jerk was diminished. Myelography revealed a large bilateral filling defect at the fourth lumbar interspace which had the appearance of a bilateral protruded intervertebral disc or possible bilateral thickening of the ligamentum flavum (Fig. 2). This patient was not operated upon because his condition developed before entering the Army. It seems apparent, however, that if operation had been undertaken on clinical grounds alone this would have been restricted to a left unilateral exploration and the pathological lesion on the right side would not have been found.

With reference to the two individuals showing evidence of diffuse intradural pathological lesions, probably arachnoiditis, the clinical diagnosis of unilateral protrusion of a lumbar disc was made in each case on the basis of a competent neurological examination. The first

Fig. 3, left. The pantopaque is diffusely scattered throughout the lumbar canal and is broken up at different levels, indicating the presence of a diffuse intradural pathological lesion (see text). Clinically the patient had presented signs and symptoms of a unilateral herniated lumbar disc.

Fig. 4. Note the diffuse breaking up of the normal pantopaque column into globules. This was constant throughout the lumbar canal. This film was taken with the patient in the erect position (see text). A clinical diagnosis of herniation of a lumbar disc had been made in this case.

patient had a history of low back pain of 4 months' duration with sciatic radiation down the posterior aspect of the left thigh, lateral aspect of the calf of the leg, and irregularly over the foot. Coughing aggravated the sciatic pain. There was marked splinting of the lumbar erector spinae muscles. Straight leg raising was very positive on the left at 20 degrees. The left ankle jerk was diminished and there was hypalgesia to pin prick over first sacral on the left anterolateral portion of the calf of the leg. There had been no symptoms referable to the right leg. The second patient gave a history of a fall 2 years previously, at which time a diagnosis of a fractured sacrum was made. This was followed immediately by low back pain and later by pain which radiated down the posterior aspect of the left thigh to its lower third. There had been repeated exacerbations of the symptoms. Anterior flexion of the lumbosacral spine was limited to

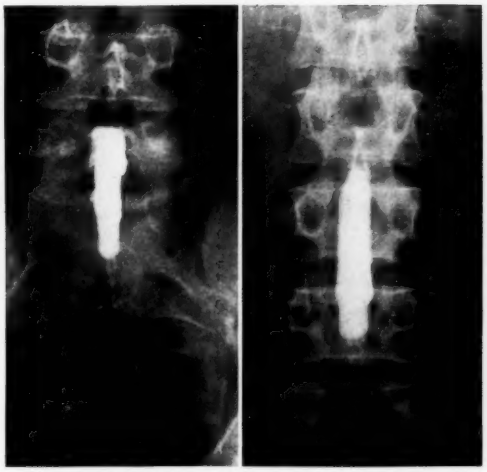

Fig. 5. a, left, Normal pantopaque myelogram at fifth lumbar interspace. b, Normal pantopaque myelogram at third lumbar interspace.

about 30 degrees from the vertical, and straight leg raising was very painful at 60 degrees on the left. There was a narrow strip of diminished sensation to pin prick over the anterolateral aspect of the left calf of the leg. The knee and ankle jerks were all sluggish and no difference between the two sides could be elicited. The patient had had no abnormal symptoms in the right leg. The myelographic findings were very similar in the above 2 cases (Figs. 3 and 4). At roentgenoscopic examination the pantopaque in both patients did not remain a compact column as it usually does when moved from level to level by tilting the table. On the contrary it became "hung up" into large globules at different levels and passed very slowly from level to level not as a column but in fine multiple trickles or strands. This type of abnormality was found in both patients to extend at least from the first to the fifth lumbar interspaces. The first patient described herein, who presented this picture (Fig. 3) was explored. A partial laminectomy was performed at the fifth lumbar interspace and the dura was opened. The arachnoid was not transparent but faintly grayish and many fine subarachnoid adhesions were noted binding together the roots of the cauda equina. The interspaces at the fourth and fifth levels were explored on the left side and no herniated

disc was found. It was our opinion that surgical intervention was unnecessary on the other patient as the diagnosis of a diffuse lesion, probably arachnoiditis (Fig. 4), was apparent and it seemed doubtful if operation could give relief.

Myelographic studies in these 2 cases demonstrated to us that our clinical diagnosis of unilateral protrusion of a nucleus pulposus was erroneous. If the clinical findings alone had been relied upon a negative exploratory operation would have been done in both cases.

In addition to diffuse intradural lesions there are, of course, other pathological conditions which may simulate a protruded disc, such as a small meningioma or perineural fibroblastoma (5, 7). Examination of the spinal canal by use of pantopaque will usually reveal such conditions.

Of the 36 cases reported it was mentioned that in 14 of these no abnormality was noted in the myelogram. We agree that a normal appearing myelogram does not rule out a herniated disc nor a "concealed" one, and in such cases it is our opinion that one must rely upon the clinical picture in determining whether or not operation is indicated.

A word of warning should be added concerning the indiscriminate use of myelography in the diagnosis of herniated disc. It is believed that such a procedure should be carried out only in those cases in which a protruded intervertebral disc is suspected on the basis of a detailed history and careful neurological examination. The myelographic study should be performed by those familiar with the procedure and qualified in its interpretation and, wherever possible, in the presence of the surgeon who is to operate upon the patient.

SUMMARY

The findings in 36 pantopaque myelograms performed on patients suspected clinically of having a unilateral protrusion of a nucleus pulposus at a low lumbar level are reported. In 2 of these patients myelography indicated the presence of bilateral protrusion of a disc, which in one case was at two different levels. In 2 of the other patients, diffuse intradural pathology, probably arachnoiditis, was demonstrated.

It is believed that these findings illustrate the unreliability of a diagnosis based on clinical signs and symptoms alone. Clinical criteria indicated the presence of a unilateral herniated disc in each case and if relied upon would have failed to reveal the presence of a herniated disc on the opposite side or an intradural pathological lesion.

If errors in diagnosis are to be reduced, it is therefore advocated that, before a patient is subjected to operation, pantopaque myelography be carried out in those cases suspected of having a herniated nucleus pulposus in the lumbar region.

Pantopaque as an agent for use in myelography has few of the objections found with those used in the past.

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MALARIA FROM BANK BLOOD TRANSFUSIONS

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THE return of military personnel from malaria infested areas to the continental United States increases the possibility of the transmission of the disease by blood transfusion. This accident has been comparatively rare, if one judges by the number of reported cases. In 1938, Wright was able to collect only 23 cases from the literature, but could add 6 of his own. Gordon found 5 more case reports, and described the first recorded instance of the production of malarial infection from the use of stored or bank blood. We wish to report 2 patients, who were infected with blood which had been refrigerated for 5 days.

CASE 1. H. F., a white woman, aged 57 years, fell on November 11, 1940, and sustained an intracapsular fracture of the left femur. She was admitted to another hospital, where the fracture was reduced and plaster fixation was applied. Two months later, malposition and nonunion were noted, and she was transferred to the Henry Ford Hospital for the insertion of a Smith-Petersen nail. This operation was performed on January 24, 1941, by Dr. C. L. Mitchell. During the open reduction, 600 cubic centimeters of citrated blood from the bank was transfused.

On the first postoperative day, there was a temperature elevation to 101 degrees. She was afebrile during the 2d, 3d and 4th weeks. On the 32d day she had a fever of 101 degrees, and again on the 35th day, the temperature was 100.6 degrees. No chills were recorded. Because the second bout of fever promptly subsided and the patient was without symptoms, she was discharged.

Two weeks later, she was readmitted to the hospital. She stated that since returning home, she had had attacks of nausea and vomiting, preceded by chilliness and sometimes actual shaking. There was a feeling of weight in the stomach and marked anorexia. The chief physical finding was the presence of tenderness and muscle spasm in the right upper quadrant. A medical consultant suggested that she might have a penetrating peptic ulcer, cholecystitis, or pancreatitis. The red blood cell count was 3,100,000 per cubic millimeter; white blood cells 2,350 per cubic millimeter; 67 per cent polymorphonuclears. Roentgen examination of the abdomen was reported as showing probable enlargement of the spleen! The significance of this observation was not immediately appreciated.

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On March 16, the 2d day of the second admission, there was a chill and a fever of 105 degrees. A smear for malarial parasites on March 17 showed some inclusion bodies not typical for the protozoa. The next day, typical organisms were seen and the diagnosis of quartan malaria was established. Quinine hydrochloride was given in 10 grain doses 3 times daily after March 20. Two days later, the temperature was 99 degrees, and it remained normal during the rest of the period of hospitalization.

The blood bank records showed that the patient had received blood which had been on hand for 5 days. The donor was a volunteer who had repaid the debt of his wife's nephew, who had just had a resection of a segment of intestine for regional enteritis. He was 50 years of age, born in Sicily. He had lived in Michigan since he was 16. At the time of the blood donation, he indicated to the questioner that he had not had malaria. However, follow-up inquiries revealed that he had had chills and fever for 4 months when he was 10 years old. He had been perfectly well for 25 years. On one occasion, after the transfusion in question, an ordinary blood smear was negative for malarial parasites.

CASE 2. A. M., a white woman, aged 23 years, was found to have bronchiectasis of the right lower and middle lobes. On May 7, 1942, the involved lobes were removed at one stage by one of us (C.R.L.). During the operation, 500 cubic centimeters of citrated bank blood were given. Her postoperative course was very satisfactory. She was afebrile from the 3d to the 22d day, at which time she was given a second transfusion on account of the presence of slight secondary anemia. Following the transfusion, there was an immediate temperature elevation to 101.6 degrees, but the next day she was afebrile. She was discharged on May 30, with instructions to keep a temperature chart.

On June 3 there was a fever of 102.6 degrees. On June 16 she reported that she was having chills and fever every 3d day. A smear for malarial parasites taken on this day was negative. On June 24 she stated that she had had no fever since the last visit. On July 5 the temperature was 104 degrees, and every 3d day thereafter until July 15 she had chills, fever, vomiting and headache. The chills started between 4:00 and 6:00 in the afternoon and lasted 5 to 6 hours. Examination of the blood at this time showed typical quartan parasites. The spleen was

palpable. She was admitted for quinine therapy, being given 10 grains of quinine hydrochloride 3 times daily. She immediately became afebrile and was discharged on July 20, with instructions to take 10 grains of drug after each meal for 6 days, and 10 grains daily for 3 months thereafter. She has remained well.

The blood bank record showed that the blood for her second transfusion was supplied by a professional donor, who had never been in a malarial district, and who had given numerous transfusions without mishap. The blood for the first transfusion was donated by a 51 year old Italian man. He was born in Sicily and had been in this country since he was 19 years old. He stated that he had never had an illness which was characterized by chills and fever. A blood smear was negative for parasites.

A common factor in our two malaria cases appeared when it was found that the donor for Case 2 was paying the blood bank debt of his nephew, who was having a second intestinal resection, his first having been responsible for the train of events which led to the infection in Case 1! It was of interest to find that the two individuals who had donated blood, both uncles of the young patient of Italian extraction, had spent their childhood in the same small Sicilian town.

It is obvious that it is possible to transmit malaria with blood which has been refrigerated for 5 days and which has been drawn from donors who have had no symptoms of the disease for 25 years. Blood which has been stored for as long as 8 days has been known to cause infection (2). The addition of quinine to the blood has been found to be without effect (1). Prophylactic administration of the drug to the recipient when questionable blood is being given has been suggested (4). The proper screening of donors is the logical means of preventing the accident of malarial transmission. Questions relating to geography would probably be more effective than those regarding past illnesses. For example, it would have been better to have asked our donors, who spoke English poorly, if they had ever lived in Sicily than to have made our routine inquiries regarding streptococcus infection, furunculosis, encephalitis, and twenty other diseases, including malaria. It is suggested that when possible, the blood of donors who have lived in malarial areas be converted to plasma.

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A STATISTICAL ANALYSIS OF A STUDY OF THE PREVENTION OF INFECTION IN SOFT PART WOUNDS, COMPOUND FRACTURES, AND BURNS WITH SPECIAL REFERENCE TO THE SULFONAMIDES

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Foreword by ALLEN O. WHIPPLE, M.D., F.A.C.S.

IN considering this report it must be emphasized that these data are based on an analysis of civilian casualties collected from 9 clinics in different parts of this country by groups of surgeons with rigid criteria of clean wound healing. The physical condition of both sexes and all ages of these casualties, the mechanism of injury, the terrain in which the injury was received, their initial and definitive treatment, were quite different from those seen in battle casualties.

In the war zones the wounds are left open. The wounded are young men in prime physical condition and with maximum resistance to infection. The wounds are frequently treated with sulfonamide powder before the soldier or sailor is transported to a hospital for definitive treatment. The terrain and cleanliness of the wounded differs very greatly in the different zones and services, e.g. the clean flyer injured in his plane, or the clean sailor rescued from the Pacific, as compared to the soldier wounded in a foxhole in fertilized fields of France or Italy. Furthermore, the criteria of wound infection and clean wound healing differ widely in the minds of the many surgeons, experienced and inexperienced, caring for battle casualties. Of necessity the condition of the wounds has to be based on their gross appearance. Colonel Churchill, consultant to the North African and Italian fronts, has very aptly said "The confusion that surrounds impressions and statistical data on wound infections is attributable in large part to differences in definition and terminology." For this reason he outlined the following 6 categories of wounds as seen in battle areas, based on the gross surgical pathological appearance of the wounds: (1) contaminated wounds, (2) wounds with surface infection, (3) surface infection with injury necrosis, (4) local invasive infection, (5) regional extension of invasive infection, and (6) generalized extension of invasive infection.

The reports that have been received from the various theaters of war on the results of sulfonamide therapy, local and general, in preventing or controlling wound infection are based largely on open wounds, with or without extensive and meticulous wound excision or débridement, and have in the main been based on impressions of the wounds for limited periods of observation without follow-up studies and without controls.

The following report is based on a sufficiently large number of civilian wounds and burns, studied by 9 groups in different hospitals in various parts of the country, to be considered statistically significant in many of the groups. Furthermore, there has been a fairly large number of controls to make groups of drug treated cases and nontreated cases comparable.

These studies demonstrate that certain factors, such as the degree and extent of the trauma, the viability of the repaired tissues, the amount of tissue tension, the type and amount of foreign bodies in the wounds, the length of time between receipt of injury and

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University.

This report has been unanimously approved by the Subcommittee on Surgical Infections and Burns of the National Research Council, Guy Caldwell, Oliver Cope, Renè Dubos, Robert Elman, Warfield Firor, Edward Howes, Sumner Koch, John Lockwood, Charles Lund, Roy McClure, Frank Meleney, and Dr. Allen O. Whipple, Chairman.

definitive treatment, the thoroughness and extent of wound revision and débridement are the determining factors in early and late wound infections and above all else prove that sound surgery is the essential factor in clean wound healing. From collateral experience with established infections we know that the sulfonamides prevent the generalized spread of infection caused by susceptible organisms especially the hemolytic streptococcus and from this experience we may assume that they do so when used prophylactically. This would seem to be further supported by the low mortality in the series presented here. Whether they prolong the period between contamination and invasion of tissues by bacteria we can only surmise. But in preventing local infection in civilian wounds these studies do not show that the sulfonamides used locally or systemically give any better results than in wounds treated with the same surgical care but without the drugs. They are therefore only an adjuvant to the treatment of infections in wounds and are in no sense a substitute for sound surgery.

Some of the committee feel that it may be expecting too much to hope that any drug will ever be discovered which will possess such a selective action on bacteria as to destroy them completely in a wound without at the same time causing serious injury to the tissues and leucocytes. Bacteriostatic agents like sulfonamides are not markedly injurious to tissue but cannot be expected to destroy completely the contaminating bacteria. In the field of antibiotics something may yet be found and should be searched for. When the adjustment of the factors in the wound is such as to permit healing with a minimum amount of disturbance of the blood supply and with a comparatively minor "destructive phase," the use of bacteriostatic agents might be of some value. However, in most wounds which are subject to closure, the effect of the drug is not of sufficient magnitude to permit total destruction of organisms by drug and phagocytes, and any foci of tissue necrosis usually become foci of bacterial growth. This conclusion points up in the most convincing way the primary importance of sound surgical methods in the management of wounds and assigns a relatively minor position to the use of the bacteriostatic agents so far available.

Because of the differences in conditions in civilian casualties as compared to those in war zones, no comparisons are made nor is any recommendation made for the use or disuse of bacteriostatic drugs as prophylactic agents in the prevention of local wound infection in war wounds. But it is the opinion of this committee that these agents should be used to prevent systemic invasion of infection. It is finally the unanimous opinion of the committee that, as always, the carrying out of the sound surgical principles of preventing and treating shock, of hemostasis, of removing nonviable tissue and foreign bodies, of repairing the wound with minimum tissue tension, of maintaining maximum nutrition to the tissues, of immobilization of the wounded part —in other words, sound surgery is the *sine qua non* of wound therapy.

Only those who have observed the work of Dr. Meleney and his associates in collecting and analyzing the data from the several units submitting reports of their results, can appreciate the untiring and honest effort that has gone into this report. As the results of other investigators in this country, Canada, and England working with the sulfonamides in the prevention of wound infection accumulate, they are corroborating the findings in this report, and the essential rôle assumed by sound surgery.

THIS is the report of the Statistical Summary for the Study of the Prevention of Infection in Contaminated Wounds and Burns under Contract OEMcmr-85 for patients admitted to the unit hospitals from January 1, 1942, to October 31, 1943. Fifteen hundred of these cases studied up to April, 1943, were briefly reported in an article which appeared elsewhere.[1]

GENERAL CONSIDERATIONS

A. The make up of the study units. Nine units have contributed to this study over a

[1]Ann. Surg., 1943, 118: 171.

period of 22 months, and the results presented herewith are based on 2,191 complete records of cases. These units were set up at the Akron City Hospital, the Charity Hospital in New Orleans, the Cincinnati General Hospital, the Cook County Hospital in Chicago, the Detroit Receiving Hospital, the Henry Ford Hospital in Detroit, the Johns Hopkins Hospital in Baltimore, the Massachusetts General Hospital in Boston, and the Presbyterian Hospital in New York. Two of these units, namely the Cook County Hospital and the Henry Ford Hospital have limited their study to burns. Three of the units discontinued the prophylactic study after the first year, the leader of one group entering the armed forces to carry on investigative work in surgical infections. The two other units turned to a study of established infections. Four units continued the study of all three categories—soft part wounds, compound fractures, and burns throughout the whole period of study and are continuing the project with the addition of three more units studying compound fractures and two more studying burns under a modified plan which will be reported later.

The steady withdrawal of personnel to active war service from the units both in the clinic and in the laboratory has made it increasingly difficult to maintain the high standards originally set for the completeness of the records and the promptness of reporting the cases to the central office. The curtailment of automobile traffic has materially cut down the incidence of civilian accidental injuries so that the total number of cases is considerably less than was anticipated at the initiation of the study. However, the consistency of the results as they have been tabulated and reported every 2 months lends weight to their significance.

B. The nature of the material. Hospitals were chosen which had available or could obtain a fair number of serious civilian accidental wounds particularly from severe automobile or industrial accidents. It was recognized that civilian accidental wounds differ from war wounds in certain respects, and any conclusions that may be drawn from them must be applied to war wounds with some reservations. The three most important differences are (1) the wide range of age and general condition of the civilian patient and the narrow age range of the soldier and his good general condition, (2) the relatively short interval between accident and operation in the civilian cases and the wide range of time interval of the soldier's wound, (3) the relatively short and atraumatic transportation of the civilian case from the scene of the accident to the hospital and the wide range of trauma to the wounded soldier during this period.

The first of these three differences would favor a high incidence of infection for the civilians. The other two would favor a high incidence of infection for the soldier. Other differences which might be considered are the relatively uniform method of treatment in the civilian hospitals in this civilian study, the compromises that must be made in the operative procedure on the soldier because of the flood of cases in a big push, the high velocity of the traumatizing agent of the soldier, the wider variations in the degree and kind of bacterial contamination of the soldier's wound because of injuries received under different climatic conditions on land, on sea, and in the air. Furthermore many soldiers will have had drug applied to their wounds over a varying period of time between the infliction of the wound and the definitive treatment. Observations on civilian cases under similar conditions would be most difficult to obtain. Of the cases included in this report it may be said in general that the burns of the civilian are most comparable to the military casualties, the compound fractures are next, and the soft part wounds are least.

In spite of these differences, it might be possible to select from these civilian cases groups which are strictly comparable with the wounded combatant but first we would have to obtain as complete data from a group of wounded soldiers. All of these points clearly indicate the complexity of the problem and the necessity for setting up a well controlled study in combat areas in which careful records can be kept of all of the relevant factors in each case which would favor or minimize the development of infection. It has been repeatedly urged by the Subcommittee on Surgical Infections and by the General Surgical

Committee that the Army and Navy both set up such a study and tentative summary sheets have been placed in the hands of Major Champ Lyons who has gone to the African and Italian theater of operations and in the hands of Captain Willian Sandusky who is in England and in the hands of Lieutenant Edwin Pulaski who has gone to the South Pacific. It is hoped that precise data may be obtained that will be made available and will be more directly applicable to the problem of the wounded combatant.

C. The focus of attention was on the sulfonamides. The study has largely concerned itself with the appraisal of certain of the sulfonamide drugs as prophylactic agents against the development of infection in civilian accidental wounds with the expectation that the results would indicate whether or not they would be useful in the prevention of infection in war wounds. The plan was first outlined by the Subcommittee on Surgical Infections in June of 1940, but for various reasons did not get under way until 18 months later. During this time some of the limitations and dangers of sulfanilamide were being recognized and the early experience with the other derivatives, particularly sulfathiazole and sulfadiazine, was being obtained. When the study actually began, it was generally agreed that sulfadiazine was the most desirable drug to use systemically because of its lower toxicity, rarer interference with kidney function, and wider range of antibacterial activity. The drugs considered best for local use were sulfanilamide and sulfadiazine.

The original plan of the study anticipated a comparison of the local with the general use of several forms of sulfonamide as well as other antibacterial agents, but the reports which came back from Pearl Harbor led the investigators to modify this plan considerably. The categories instead of being twelve as originally planned were narrowed down to two or three. The principal category was treatment with systemic sulfadiazine combined with equal parts of sulfanilamide and sulfadiazine locally. This regimen was followed by all units for the first 6 months. Following this the local treatment was changed to sulfanilamide. Six months later still, the local treatment was given up almost entirely and observations were made on systemic sulfadiazine alone. Thus three principal methods of sulfonamide treatment have been appraised.

D. The problem of controls. A great deal of time and thought and discussion was given to the question of adequate controls. It was recognized at the beginning that any valid comparison between drug treated and non-drug treated patients would have to consider whether the injuries in the two groups were of the same severity, whether the bacterial contamination was of similar extent, whether the delay in operation following injury was of similar duration, etc., etc. Ideally all of the factors favoring or minimizing the development of infection should be equally distributed throughout the two groups. The difficulties of obtaining strictly parallel controls was fully recognized. The director of one of the units stated that physicians referring patients from the industrial plants in the neighborhood would require the use of sulfonamides for the treatment of their employees and that controls would not be possible to obtain. It was pointed out that no purpose would be served by carrying on a study without controls, for there would be no basis for comparison and the benefits from the drugs would be assumed but not proved. It was therefore decided that controls should be used where they could be obtained and these controls would have to serve for the whole series. Three units therefore started with no controls, in the others, two methods of treatment were compared by alternating the cases as completely as possible. In several of the units there were at times three methods of treatment tried in rotation. This was recognized as a cause for a certain amount of heterogeneity in the results obtained from the different units. Other causes that were recognized were: (1) no one hospital would have a fair sample of all of the different types of cases which would exist in different parts of the country; (2) no one hospital would have enough cases of one kind in a year's time to have a significant series; (3) the bacteriological flora would probably differ in different parts of the country and at different seasons; (4) no one hospital would be able to give

what might be called "average care" of the patient with regard to aseptic technique; (5) no one group of surgeons would give "average surgical care" to the patients either at operation or at dressings; (6) no one group of observers would be completely free from individuals having preconceived ideas regarding the value of one or another method of treatment.

Before the initiation of this study therefore it was recognized that this complex problem could not be solved by any one group of observers working in any one place or institution. So it was decided to set up as many units as could be properly handled and pool the results in order to balance these differences and minimize the "personal equation."

However, it would take a large number of units to balance evenly all of the elements of the personal equation, and it was not expected that this would be accomplished, although it might be approached by setting up ten or a dozen units. The operation of these units in various parts of the country of itself might be expected to yield heterogeneous results but by pooling them it was believed that a homogeneous or at least a composite picture of real value might be produced.

E. Method of gathering data (the summary sheet). The method of collecting and analyzing the data from these widely scattered units was of course extremely important. The extent of heterogeneity could be determined only by recording in every case, all of the essential factors concerned with wound infection. This required the careful preparation of a summary sheet in the compilation of which the committee had the advice of Dr. Crosby of Johns Hopkins, Miss Kurtz of the Presbyterian Hospital Record Room, and statisticians from the Medical Departments of the Army and Navy. A copy of this sheet will be sent to anyone requesting it.

It is seen that the conditions which were present at the time of the injury, during transportation to the hospital, in the hospital before operation, the findings at operation, the procedures, the results of laboratory studies, particularly the bacteriological analysis, the postoperative course, and the development of clean wound healing or infection, may all be recorded in such a way that they can be transferred to punch cards. The relevant data were transferred from the hospital records to these summary sheets. One copy was kept by the unit and the other sent to the central office in New York for analysis together with records from the other units. The summary sheets were then scrutinized carefully by the statistical secretary and rechecked by the responsible investigator under this contract. When omissions or inconsistencies were found, the matter was referred back to the director of the unit concerned and the necessary corrections were made.

When the sheet of any individual case was found to be complete, the data on each sheet were transferred to a punch card for the purpose of statistical analysis. The International Business Machines Company's sorting and counting machine has been used for this purpose. During the course of the study, preliminary results have been reported to the assembled responsible investigators, clinical directors, and members of the committee and interested Army and Navy medical representatives and others who have met in Washington every month or two for purposes of discussing the work of the Subcommittee on Surgical Infections. The present report deals with the data in considerably more detail than previous reports but still does not include many tables prepared from work sheets based upon groupings which were made to test out the significance of relatively minor factors. Such studies could be carried out almost *ad libitum* but the presentation of such tables would be confusing rather than clarifying and an endeavor has been made to present only those tables of major importance which seem to tell the story.

F. The method of analysis. In analyzing the data which have come in on the summary sheets, the wise counsel of Dr. Lowell Reed, chairman of the Committee of Biostatistics of The National Research Council has been given with regard to general principles. Dr. John Fertig, a member of his committee and professor of biostatistics of the Delamar Institute of Columbia University has studied the figures, checked their significance, and given valuable advice with regard to their presenta-

tion. In his discussion of the problem he writes as follows particularly with regard to the comparability of the controls with drug-treated cases:

"Speaking generally, if a group of controls and a treated group should show the same distribution with respect to all apparently relevant items, it might not be unfair to compare the gross results. Here, however, we find that the two groups do show a rather marked difference with respect to some factors, so that the gross comparisons are not completely valid. Furthermore, even should the two groups be distributed somewhat to the same extent on the bases of the factors listed here in the tables of crossclassification, that would not insure that they were equitably distributed with respect to other factors. Admittedly, if the two groups seem to be equitable with respect to a large number of possible factors, they might be compared with some degree of assurance.

"In our case it seems that one way out of the difficulty is not to rely on the gross comparisons, but to make the comparisons of the drug and control series specific for a group of factors apparently important in the determination of infection singly or preferably simultaneously. Thus, for example, we may compare the control and drug specifically for a given amount of tissue damage and a given amount of contamination simultaneously, since these two factors appear to be relevant in the subsequent course of wound healing. This gives us a number of comparisons instead of one gross comparison. The controls and treated cases with a given grade of both factors may still not be completely comparable with respect to other factors such as wound area, distribution with respect to units, etc., but they are quite apt to be far more comparable with respect to other factors than were the original two series *in toto*, and certainly they are comparable with respect to the two factors considered. One more factor worked into a crossclassification scheme would insert one further element of comparability and render even further removed the possibility of a consistent heterogeneity running through all the comparisons. Again, the more intensive the crossclassification, the smaller the frequencies in any particular subgroup, with the result that individual comparisons will have little merit *per se* because of the tremendous magnitude of chance errors. In such cases, of course, reliance cannot be put on any particular specific comparison but rather on the series of comparisons as a whole."

This advice has been followed and although gross comparisons have been made on Tables IV (soft part wounds) and XXXIII (compound fractures), emphasis has not been placed upon them but attention has been focused on the comparisons of drug treated cases with the controls in groups having one, two, or three common factors which seem to be related to wound infection.

Wherever possible, the formulae of the biostatisticians have been applied to the percentage figures. The formula generally used has been that which was recommended for surgeons by Campbell in his article[1] entitled "The Statistical Method."

The formula indicates whether or not percentage differences are statistically significant, minimizing the element of chance. The results are the same whether the figures are given for the percentage of infection or the percentage of clean wound healing. Inasmuch as this study is directed toward lowering the incidence of infections, the figures for infection have been used in the accompanying tables. Significant differences have been indicated by the letter S.

Where complete data have not been available in any given case so that the totals do not reach the sum total of cases in any group, this has been indicated by an asterisk. For one reason or another certain of the relatively unimportant factors were occasionally omitted from the records.

G. The surgical care of the patients. In setting up the study units, the difficulties of obtaining well trained personnel was recognized. Many of the clinical surgeons and laboratory workers originally chosen in June of 1940 were called away to active military service in the course of the 18 months of delay in starting the project.

With regard to the surgical care of the patients, no attempt was made to straight jacket the surgeons beyond the requirement that all of the patients were to be treated as surgical emergencies and were to be operated on as soon as it was physically possible with as complete a removal of the dead or injured tissue as the severity of the accident indicated. For this procedure we have used the term "débridement." Furthermore the patients were to be treated with all of the modern methods at the disposal of the units for the care of shock and other operative and postoperative sequelae and complications associated with such cases.

[1]Surgery, 1941, 9: 825.

H. The bacteriological studies. An attempt was made to work out a complete bacteriological analysis of the tissue removed from the wound at the time of the primary operation. It has been difficult at times to separate out from a mixed flora all of the species present and obtain them in pure culture. The usual methods of wound culture, namely rubbing a cotton swab on the wound surface and incubating it aerobically, in broth or even snipping bits of tissue and culturing them aerobically and anaerobically, are obviously not enough. An accidental wound is contaminated by bacteria carried in for the most part on foreign bodies which are scattered here and there throughout the wound. A knowledge of the potential agents of infection can be obtained only by taking all of the material removed at débridement and recovering representative members of all contaminating species. This means of course that the bacteriologists concerned must have some knowledge of the whole range of bacteriology both aerobic and anaerobic, and pathogenic as well as nonpathogenic, for almost any kind of organism may contaminate a wound.

Realizing the probable limitations of the laboratory personnel which would be available, it seemed advisable not only to have standard procedures and uniform media and an acceptable nomenclature for all of the units but also to set up a central laboratory with a recognized authority in charge, to whom all of the difficult problems which might arise, could be referred. Further details of this plan and the degree of success obtained will be the subject of a supplementary report prepared by Dr. Ivan C. Hall, the director of the Central Laboratory which was set up in New York at the College of Physicians and Surgeons.

We ordinarily think of different species of bacteria as being pathogenic or nonpathogenic but these are not absolute terms. There are many nonpathogenic strains among a pathogenic group such as the beta hemolytic streptococci and the establishment of infection in a wound depends not only on the number and virulence of the organism but on the conditions of local and general defense present in or developed by the body at the site of the bacterial contamination. This has been amply confirmed by the present study. In many cases so called pathogenic species have been cultured from the débrided tissue which never gave rise to clinical infection and at the same time some cases developed infection in which only nonpathogenic organisms were originally found. This does not mean that the organisms are not the essential elements of infection but (1) that there are other important factors concerned in the development of infection, (2) that there are antagonisms as well as synergisms among the bacteria entering a wound, (3) that there are opportunities for secondary contamination from the environment of the patient, and (4) that there are limitations to the knowledge of even the most expert bacteriologist.

In the analysis of the bacteriological data, it seemed to be important to show the relationship between the development of infection and the incidence of various organisms in the débrided tissue as well as in later wound cultures with particular reference to the treatment which the case received.

Those cases have therefore been taken as separate groups in which the hemolytic streptococcus or coagulase positive Staphylococcus aureus or other coagulase positive micrococci, or pathogenic gram-negative bacilli, or Clostridium welchii, or anaerobic streptococci, were found in the débrided tissue. The number of these cases in which clinical infection developed has been noted. The number of these cases in which these organisms persisted and likewise the number of cases in which they were found later during the course of wound healing although not found in the original cultures of the débrided tissue, have been determined. Each of these groups has been further subdivided according to the local and general chemotherapy which they received in order to find out whether the drugs were able to help the body rid the wound of the original contamination or prevent the later establishment of organisms secondarily introduced.

I. The definition of infection. Attention has been focused upon the process of wound healing with particular reference to the development of *infection*. This has been defined as "the reaction of the tissues in and about the

TABLE I.—INCIDENCE OF INFECTION IN THE WHOLE SERIES OF 2191 CASES UNDER STUDY DIVIDED INTO THE THREE MAIN CATEGORIES

	Totals	Per cent infection
Soft part wounds		
Totals	926	
Serious infection	59	6.4
Trivial infection	104	11.2
		17.6
Compound fractures		
Totals	674	
Serious infection	95	14.1
Trivial infection	77	11.4
		25.5
Burns		
Totals	591	
Serious infection	129	21.8
Trivial infection	146	24.7
		46.5

wound to the presence of micro-organisms or their poisons." Infections have been graded as serious or trivial—the former being those which showed general symptoms, or further destroyed tissue or materially prolonged the period of wound healing or hospitalization. The determination of the presence and severity of infection has been the consensus of all of the doctors in charge of the patient and while there may have been a difference of opinion in borderline cases, the decisions must be considered reasonably accurate and consistent with the other evidence in the case.

One may very properly say that it is only the serious infections that deserve consideration, but it must be remembered that the line between serious and trivial is not sharp. It is of interest to note, however, that the statistically significant differences are for the most part in the serious groups.

We wish to make clear, therefore, that the criteria of infection in this study have not been based upon the finding of bacteria in the wound, either at the start or later in the course of wound healing but upon the clinical evidence of the response of the body to the presence of those organisms.

J. The gross results of the study. In the whole study there are 2,191 cases analyzed, of which there are 926 soft part wounds, 674 compound fractures, and 591 burns. Table I shows the incidence of serious and trivial infections in these main groups. Each group has been analyzed further by dividing it into two or three subgroups from the point of view of the presence or absence of certain common factors which might favor or minimize the development of infection. For example all of the patients operated on within 3 hours of the accident have been compared with those operated on after 3 hours to bring out the difference between early and late operation. Similarly all of those with greater gross contamination of the wound as found at the time of operation have been compared with those having lesser gross contamination. Likewise all of those with greater tissue damage have been compared with those having lesser tissue damage,—and so on with many relevant factors.

By gross contamination is meant the amount of dirt or other extraneous material the surgeon found in the wound at the time of the operation. By tissue damage is meant the amount of dead or injured tissue the surgeon found. They were classified in each case as none, slight, moderate, and severe. The first two were considered lesser and the last two greater. These comparisons tend to bring out the importance of certain factors which we have suspected for a long time of playing a rôle in favoring or minimizing wound infection. The study, however, was undertaken *not* to weigh or measure the relative importance of these factors but *to find out what methods of treatment could prevent the development of infection.* In analyzing these cases, therefore, attention has been focused primarily on the results obtained by the sulfonamide drugs.

The records will be available indefinitely to any responsible individual who wishes to pursue any lead in any direction which has not been fully covered in this report.

K. Limitations of the scope of the study. It is recognized that this study does not include observations on wounds treated immediately with local drugs and delayed operation, such as might occur under battle conditions. This was discussed in several committee meetings and it was thought inadvisable to delay the operative procedure in our hospital cases unless shock demanded it. In a few cases at one hospital surgical treatment was delayed but the data are insufficient for satisfactory anal-

ysis. The evaluation of this form of treatment will have to await the setting up of study groups in combat areas. The only report from the front so far available to the writer is that by Elliot Cutler in a series of something over a hundred cases with an equal number of controls which showed the same percentage of infection in cases treated with drug as in the controls. His results were very similar to our own figures. The report of Ferguson from the Pacific and others from the Mediterranean theater lack concurrent observations on nondrug treated controls.

L. Acknowledgments. In this report on the appraisal of the sulfonamides in accidental civilian wounds of the soft parts, compound fractures and burns, all of those who have worked in the wards and in the laboratories, doctors, nurses, bacteriologists, chemists, and technicians have a share. Likewise those who have labored over the records to make them as complete and accurate as possible have contributed an invaluable service. It has been a co-operative effort of considerable magnitude. The writer would particularly like to thank Miss Kurtz, of the Presbyterian Hospital Record Room, and Dr. Crosby, of Johns Hopkins, for their aid and advice in the formulation of the summary sheets and Miss Kurtz for her technical advice on sorting and analyzing the data throughout the study. The chief burden of sorting and assembling the data, scrutinizing every detail of the summary sheet, etc., has fallen upon Miss Eleanor Harrison, the chief statistical secretary, and her assistants, Miss Ann Talbot, Mrs. Margaret Cooper, and Miss Josephine Mannino. All of these data have been checked and rechecked many times by the secretaries and the responsible investigator, and finally reviewed in detail by Dr. John Fertig. To all of these individuals and to the responsible investigators[1] and clinical directors[2] as well as to Dr. Evarts Graham, Chairman of the Committee on Surgery, and Dr. Allen O. Whipple, Chairman of the Subcommittee on Infected Wounds and Burns, of the National Research Council, the writer extends his hearty thanks.

[1]Responsible investigators: Warfield Firor, Charles Johnston, Sumner Koch, John Lockwood, Perrin Long, Champ Lyons, Roy McClure, Frank Meleney, Alton Ochsner, Mont Reid, Clair Vale and Max Zinninger.

[2]Clinical directors: William Altemeier, Eleanor Bliss, Robert Elliott, Henry Harkins, John Hirshfeld, Max Kepl, Conrad Lam, Alfred Longacre, Frederick Rhinelander, Edward Watson, and William White.

TABLE II.—A BREAKDOWN OF THE CASES OF SOFT PART WOUNDS ACCORDING TO UNITS, WITH PARTICULAR REGARD TO THE INCIDENCE OF INFECTION IN CASES OF DRUG-TREATED PATIENTS AND IN CONTROLS

Hospital units	Total cases	Sulfonamide cases			Controls		
		Number of cases	Per cent infection		Number of cases	Per cent infection	
			Serious	Trivial		Serious	Trivial
Akron City	65	52	3.8	15.4	13	7.7	7.7
Charity, New Orleans	180	140	10.7	10.0	40	15.0	15.0
Cincinnati General	246	173	10.4	8.1	73	2.7	6.9
Detroit Receiving	230	72	1.4	18.1	158	3.8	6.3
Johns Hopkins	57	56	3.6	28.6	1	00.0	00.0
Massachusetts General	38	36	2.8	27.8	2	00.0	50.0
Presbyterian, N.Y.	110	75	6.7	5.3	35	00.0	5.7
Totals	926	604	7.3	13.1	322	4.7	7.8

SOFT PART WOUNDS

There were 926 soft part wounds with an incidence of 6.4 per cent serious and 11.2 per cent trivial infections or a total of 17.6 per cent. This is three or four times as many infections as occur in clean operative wounds in any well ordered hospital. In the accompanying tables the cases have been divided in subgroups to bring out the importance of various factors. In Table II the cases have been presented according to hospital units particularly with respect to the incidence of infection in the drug treated cases and in the controls. It will be seen that there are real discrepancies but they tend to balance one another to a certain degree. For example at Cincinnati and Charity Hospitals the serious infections outnumber the trivial while at the Detroit Receiving Hospital, Johns Hopkins, and at Massachusetts General the trivial far outnumber the serious and in the group as a whole the trivial are almost twice as frequent as the serious. It is obvious from this table that we cannot too sharply differentiate the serious from the trivial, for the line between them is not sharp and they both represent a

TABLE III.—MAJOR FACTORS CONCERNED WITH WOUND INFECTIONS

	Totals	Per cent infection			
		None	Serious	Trivial	Total
Multiple wounds	300	75.8	7.7	S.16.5	S.24.2
Single wounds	626	85.4	5.8	S. 8.8	S.14.6
Stab wounds	257‡	84.1	5.8	10.1	15.9
Greater gross contamination	322	76.0	S.10.3	13.7	S.24.0
Lesser gross contamination	604	85.8	S. 4.3	9.9	S.14.2
Greater tissue damage	425	77.0	S. 8.3	S.14.7	S.23.0
Lesser tissue damage	501	87.0	S. 4.8	S. 8.2	S.13.0
Operation after 3 hours	365*	78.9	S. 9.9	11.2	S.21.1
Operation before 3 hours	556*	84.8	S. 3.9	11.3	S.15.2
Large area	148	71.6	7.4	S.21.0	S.28.4
Small area	778	84.4	6.2	S. 9.4	S.15.6
Incomplete débridement	270*	76.6	S. 9.3	S.14.1	S.23.4
Complete débridement	607*	89.6	S. 4.1	S. 6.3	S.10.4
Incomplete removal of foreign body	70*	81.4	7.2	11.4	18.6
Complete removal of foreign body	111*	82.0	3.6	14.4	18.0
Irrigation for over 10 minutes	203	72.4	8.9	S.18.7	S.27.6
Irrigation for less than 10 minutes	723	85.2	5.7	S. 9.1	S.14.8
No closure of wound	76	81.3	S. 6.7	S.10.7	S.17.4
Complete closure of wound	759	85.9	S. 5.5	S. 9.9	S.15.4
Partial closure of wound	72	59.7	15.3	25.9	40.3

S. Statistically significant differences.
*In certain cases these data were not recorded.
‡Some stab wounds were single and some multiple.

TABLE IV.—SHOWING THE RESULTS IN SOFT PART WOUNDS OF CLOSURE WITH AND WITHOUT TENSION

		Wound closure		
		With tension	Without tension	Not recorded
Complete closure Totals		71	536	172
Per cent serious infection	S.	16.9	4.5	4.1
Per cent trivial infection	S.	16.9	8.2	12.2
Partial closure Totals		12	38	22
Per cent serious infection	S.	25.0	13.2	13.6
Per cent trivial infection	S.	25.0	15.8	40 9

S. Statistically significant differences.

breakdown of our efforts to prevent the activity of the contaminating organisms.

The variability of the results in the different units is probably chiefly indicative of the variability of the material and the conditions found in the different hospitals but the possibility that there was some degree of difference of interpretation of the terms "serious" and "trivial" infections cannot be denied in spite of the frequent discussions on this point at the meetings of the committee.

Even for those units having an appreciable number of controls, the difference of per cent infected between drug treated and controls is at variance. Such variations do not invalidate the results but emphasize the importance of the statement made in the introductory paragraphs that in order to arrive at reliable conclusions, the experience of all of the units has to be pooled and then regrouped according to the presence or absence of relevant factors. Thus the only safe comparisons must be drawn from the series of differences emanating from crossclassifications.

Table III takes the group as a whole and divides it into either two or three subgroups to bring out some of the chief factors associated with infection. It is seen that there is a high incidence of infection in multiple wounds as compared with single wounds; in wounds which had greater gross contamination as compared with those with lesser gross contamination; in those with greater tissue damage as against those with lesser tissue damage; in those operated on later than 3 hours as contrasted with those operated on within that period; in large versus small wounds; in those with incomplete as against those with complete débridement; in long versus short irrigation and in partial closure of the wound as compared with complete closure or no closure. In most of these categories we have confirmed statistically what we have learned from clinical experience regarding the main factors concerned with the development of, or resistance to, infection. It is of interest to note that significant differences in the total percentage of infection are found in all but one of these listed here. These differences are either in the serious infections or in the trivial and sometimes in both. Many other factors have been analyzed but seem to be less important,—for example shock, drainage of the wound, and involvement of the peritoneal cavity and the

TABLE V.—INCIDENCE AND PERCENTAGE IN SOFT PART WOUNDS OF SERIOUS AND TRIVIAL INFECTIONS IN THE CONTROLS AND IN CASES OF PATIENTS WITH THE VARIOUS FORMS OF DRUG TREATMENT

	Cases	Number of infections			Per cent of infection		
		Serious	Trivial	Total	Serious	Trivial	Total
Total number of cases	926	59	104	163	6.4	11.2	17.6
Neither general nor local sulfonamide	322	15	25	40	4.7	7.8	S.12.4
Total sulfonamide	604	44	79	123	7.3	13.1	S.20.4
General without local	153	15	12	27	9.8	7.8	17.6
General with local sulfanilamide and sulfadiazine	187	8	26	34	4.3	13.9	18.2
General with local sulfanilamide	225	20	39	59	8.9	17.4	26.2
Miscellaneous sulfonamide	39	1	2	3	2.6	5.1	7.7

S. Statistically significant differences.

alimentary tract. All of these groups need further breakdown for other factors play important rôles in each of these categories which may weight the figures one way or another so as to disturb the comparability of the main groups. For example, one might expect the group with prolonged irrigation of the wound to include a larger number of cases with maximum gross contamination than the group with a short period of irrigation; so these groups must be subdivided and cross tabulated.

Table IV shows a cross tabulation between closure of the wound and tissue tension. In some of the earlier cases this factor was not recorded. It is apparent that tension, or the conditions which led to its use, with both the partial and complete closure of wounds after débridement, played an important rôle in the development of infection, but we can find no evidence that the use of sulfonamide modified this result in any way. It is to be noted that the incidence of infection is higher in the partially, than in the completely, closed wounds. This suggests not only that these wounds were exposed to secondary contamination but that partial closure was a compromise with infection, possibly done only when it seemed necessary to cover up important structures.

TABLE VI.—PERCENTAGE IN SOFT PART WOUNDS OF CASES IN DRUG TREATED PATIENTS AND CONTROLS WHICH HAD THE MAJOR FACTORS FAVORING WOUND INFECTION

		Totals	322 Controls, per cent	Totals	604 Sulfonamides, per cent
Greater contamination		103	32.0	219	36.1
Greater tissue damage	S.	127	39.4	298	49.5
Operation after 3 hours		38	11.9	96	16.0
Incomplete débridement	S.	78	24.2	192	31.8
Prolonged irrigation	S.	57	17.7	146	24.2
Large wound area		49	15.2	99	16.4
Partial closure of wound	S.	9	2.8	63	10.4

S. Statistically significant differences.

Table V takes the group as a whole (without regard to the factors favoring infection) and divides it into controls and the three main categories of drug treated cases together with a small group of miscellaneous drug treatments.

This table shows that the results in the three main categories of drug treatment yielded no significant differences. The very small series of miscellaneous treatments shows a significantly smaller number of infections but for various reasons these cases are not comparable with the others, and one cannot conclude that the miscellaneous drug treatments are any better than the three regularly employed. This similarity of the three main drug groups runs through all of the cross tabulations and it seems to be of particular interest that the combined general and local use of drug is no better than the systemic administration alone. With no difference in results shown between the three methods, one can therefore in the subsequent tables to be presented, pool the whole drug treatment experience, and consider it against the control experience. This comparison seems to indicate that the control patients did significantly better than the treated patients with a total of 12.4 per cent of infections as compared with 20.4 per cent among the drug treated patients. Does this mean that the drugs did more harm than good?

To consider this point one has to know whether the controls are strictly comparable

TABLE VII.—INDICATING THE SEVERITY OF THE INJURY BY THE DEGREE OF PENETRATION OF THE WOUND OF SOFT PARTS WITH PARTICULAR REFERENCE TO THE INCIDENCE OF INFECTION IN CASES OF DRUG TREATED PATIENTS AND IN THE CONTROLS

	Controls				Sulfonamide cases			
	Totals	Per cent infection			Totals	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Skin and subcutaneous tissues only	51	3.9	9.8	13.7	60	3.3	13.3	16.6
*Muscles or tendons	S.241	5.4	7.5	12.9	405	6.9	14.3	21.2
Nerve injury	S. 37	2.7	8.1	10.8	63	6.4	17.5	23.9
Serous cavity	S. 31	3.2	6.5	9.7	150	10.0	12.7	22.7
Joint cavity	10	10.0	10.0	20.0	29	10.3	17.3	27.6
Respiratory tract	11	00.0	00.0	00.0	25	8.0	12.0	20.0
Alimentary tract	8	00.0	00.0	00.0	85	14.1	17.7	31.8
Urinary tract	0	00.0	00.0	00.0	12	33.3	00.0	33.3
Heart or great vessels	1	00.0	00.0	00.0	13	15.4	15.4	30.8
Brain or spinal cord	0	00.0	00.0	00.0	2	00.0	50.0	50.0
Other sites	20	10.0	5.0	15.0	59	18.7	23.7	52.4

*Many of these cases duplicate others.
S., Statistically significant differences.

TABLE VIII.—SOFT PART WOUNDS: COMPARISON OF CASES IN DRUG TREATED PATIENTS AND CONTROLS WITHIN SUBGROUPS COVERING FIVE OF THE MAJOR FACTORS CONCERNED WITH WOUND INFECTION

Major factors	Controls				Sulfonamide cases			
	Totals 322	Per cent infection			Totals 604	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater gross contamination	103	7.8	10.7	18.5	219	11.4	15.0	26.4
Lesser gross contamination	S.219	3.2	6.4	9.6	385	4.9	12.0	16.9
Greater tissue damage	127	7.1	12.6	19.7	298	8.7	15.8	24.5
Lesser tissue damage	S.195	3.1	4.6	7.7	306	5.9	10.5	16.4
Incomplete or no débridement	98	10.2	7.1	17.3	221	8.6	15.4	24.0
Complete débridement	S.224	2.2	8.0	10.2	383	6.5	11.8	18.3
Irrigation more than 10 minutes	57	7.0	15.8	22.8	146	9.6	19.9	29.5
Irrigation less than 10 minutes	S.265	4.1	6.0	10.1	458	6.6	10.9	17.5
Late operation more than 3 hrs.	38*	10.5	13.2	23.7	96	11.5	10.4	21.9
Early operation less than 3 hrs.	S.282*	3.5	7.1	10.6	504	6.6	13.7	20.3

*Data missing in 6 of these cases.
S., Statistically significant differences.

as a group with the drug cases, with respect to those factors which tend to favor infection as indicated on Table III. Table VI shows the percentage of several of those factors in each of the two groups. It is seen that drug treated cases included a higher percentage of each of those factors than the controls. Several of these percentage differences are statistically significant and the others are not but all point in the same direction and seem to indicate that the controls as a group were somewhat less serious. One cannot tell from the figures whether or not these differences with regard to severity, completely offset the differences in the infection percentages of the two groups seen in Table V.

These two tables (V and VI) which point in different directions, clearly illustrate the point made in the preliminary paragraphs,—that gross comparisons may lead one astray and they emphasize the necessity for making comparisons within groups having one or more common factors. Cross tabulations have been carried out for this purpose and appear on Tables VII, VIII, IX, and X.

Some idea may also be gained of the severity of these accidental wounds by a study of Table VII, which indicates the depth of wound penetration with relationship to the drug treatment. The early impressions that the sulfonamides were of particular value in serous cavities—particularly in the peritoneal cavity which has been soiled by intestinal organisms, led to their more frequent employment in these areas. In the whole study the ratio of drug treated cases to the controls is about 2 to 1 but in some of the categories shown in Table VII it is 5 to 1 or even 10 to 1. Nevertheless, this offers an opportunity to compare the drug treated cases and the controls in groups in which a common factor is operating. In this table there are many duplications. Most of the wounds involved consid-

TABLE IX.—SOFT PART WOUNDS: COMPARISON OF CASES IN DRUG TREATED PATIENTS AND CONTROLS WITHIN SUBGROUPS CONTAINING TWO COMBINED MAJOR FACTORS WHICH ARE CONCERNED WITH WOUND INFECTION

Major factors combined	Controls				Sulfonamide cases			
	Totals	Per cent infection			Totals	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater contamination and greater tissue damage	66	7.6	13.6	21.2	154	13.0	16.9	29.9
Greater contamination and lesser tissue damage	37	8.1	5.4	13.5	65	7.7	10.8	18.5
Lesser contamination and greater tissue damage	61	6.6	11.5	18.1	144	4.2	14.6	18.8
Lesser contamination and lesser tissue damage	S.158	1.9	4.4	6.3	241	5.4	10.3	15.7
Greater contamination and irrigation >10 min.	22	13.6	22.8	36.4	74	10.8	24.4	35.2
Greater contamination and irrigation <10 min.	81	6.2	7.4	13.6	145	11.7	10.4	22.1
Lesser contamination and irrigation>10 min.	35	2.9	11.4	14.3	72	8.3	15.3	23.6
Lesser contamination and irrigation<10 min.	S.184	3.3	5.4	8.7	313	4.2	11.2	15.4

S., statistically significant differences.

TABLE X.—SOFT PART WOUNDS: COMPARISON OF CASES OF DRUG TREATED PATIENTS AND CONTROLS WITHIN SUBGROUPS CONTAINING THREE OF THE MAJOR FACTORS COMBINED, WHICH ARE CONCERNED WITH WOUND INFECTION

Major factors combined	Controls				Sulfonamide cases			
	Totals	Per cent infection			Totals	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater contamination, greater tissue damage and incomplete débridement	13	30.7	15.4	46.1	53	15.1	22.7	37.8
Lesser contamination, lesser tissue damage and complete débridement	S.107	00.0	3.7	3.7	145	6.2	9.0	15.2
Greater contamination, greater tissue damage and irrigation over 10 min.	18	5.6	27.8	33.4	64	10.9	28.2	29.1
Lesser contamination, lesser tissue damage and irrigation less than 10 min.	S.140	2.1	2.9	5.0	211	4.3	9.5	13.8
Greater contamination, greater tissue damage and operation after 3 hours	6	16.7	33.3	50.0	30	23.3	6.7	30.0
Lesser contamination, lesser tissue damage and operation before 3 hrs.	S.139	1.4	4.3	5.7	205	5.9	10.3	16.2

S., statistically significant differences.

erably more than just the skin and subcutaneous tissues. Nerves and tendons were frequently involved together and muscles were injured along with most of the serous cavities. The infection figures reveal in every category a higher percentage in the drug treated cases than in the controls and several of these differences are statistically significant. It is of interest also that among the controls there were 8 cases involving the alimentary tract without an infection among them.

In Table VIII the cases are divided in such a way that the drug treated cases and controls can be compared within subgroups featuring certain factors which are thought to be of major importance with respect to the development of wound infection. It is seen that in every category with one close exception in the smallest group, the total percentage of infections was higher in the drug treated cases than in the controls. In all but one instance in each, this held true for both serious and trivial infections. It will be noted throughout the table that the number of cases with factors favoring infection are smaller than those without those factors in both the drug treated series and the controls. This may be an indication that these civilian cases are as a whole group less serious injuries than might be available for a study among wounded soldiers. When the biostatistician's formula is applied to the figures in this table, it is seen that the difference between the figures for the controls and the drug treated cases is statistically significant and in favor of the controls only for those cases in which the factors favoring wound infection is minimal. However, in the

TABLE XI.—SOFT PART WOUNDS: DAY OF ONSET OF SERIOUS AND TRIVIAL INFECTIONS CORRELATED WITH THE DRUG TREATMENT AND WITH THE CONTROLS

		Not counted	Counted	Per cent of infections starting on days indicated			
				5 or less	6–10 days	11–15 days	over 15 days
Total infections	163						
Serious	59	5*	54	42.6	31.5	18.5	7.4
Trivial	104	18*	86	27.9	43.0	15.1	14.0
No sulfonamide: Total infections	40						
Serious	15	1*	14	50.0	28.5	14.3	7.2
Trivial	25	2*	23	26.1	56.5	13.0	4.4
Sulfonamides: Total infections	123						
Serious	44	4*	40	40.0	32.5	20.0	7.5
Trivial	79	16*	63	23.6	38.2	15.9	17.5

*Time of onset of infection not recorded.

other groups although the differences are not statistically significant; they all point in the same direction with one close exception in the smallest group; this direction favors the controls.

It is possible that there are factors still operating within these groups to make the controls and the drug treated cases uncomparable such as the factor of severity. This warrants a further breakdown into groups containing two or more factors simultaneously. Such a cross tabulation furnishes data for Table IX in which two major factors are combined in a single group, thus lessening the chance of heterogeneity. In this table also is found a consistency which is significant. In all but one line of figures (which represents the smallest group) the percentage of total infections for the drug treated cases is higher than that of the controls. In two others the serious infection rate in the controls is slightly higher than in the drug treated cases but this difference is offset by a lower rate in the trivial infections. In only two categories are the numbers large enough and the differences great enough to be statistically significant and are in favor of the controls, but the general trend is also significant and is not in favor of the sulfonamides.

Table X illustrates a further breakdown into categories combining three of the major

TABLE XII.—SOFT PART WOUNDS: INCIDENCE OF INFECTION IN CASES YIELDING THE MAIN GROUPS OF PATHOGENIC BACTERIA IN CULTURES OF THE DÉBRIDED TISSUE

	Totals	Per cent infection			
		None	Serious	Trivial	Total
Hemolytic streptococcus: Found in cultures	53	60.4	S.15.1	S.24.5	S.39.6
Not found in cultures	873	83.8	S. 5.8	S.10.4	S.16.2
Total	926	82.4	6.4	11.2	17.6
Coagulase positive Staphylococcus aureus: Found in cultures	73	71.2	S. 9.6	S.19.2	S.28.8
Not found in cultures	853	83.3	S. 6.1	S.10.6	S.16.7
Total	926	82.4	6.4	11.2	17.6
Pathogenic aerobic gram-negative bacilli: Found in cultures	147	72.1	S.14.3	13.6	S.27.9
Not found in cultures	779	84.3	S. 4.9	10.8	S.15.7
Total	926	82.4	6.4	11.2	17.6
Clostridium welchii: Found in cultures	138	76.8	9.4	13.8	23.2
Not found in cultures	788	83.4	5.8	10.8	16.6
Total	926	82.4	6.4	11.2	17.6

S., statistically significant differences.

factors concerned with wound infections but only those combinations are shown in which these three are either all maximal or all minimal. As the numbers in any one group decrease, the variations become greater. In the three smallest groups the differences slightly favor the sulfonamides but these differences are not statistically significant. In the three largest groups the differences are significant and favor the controls but these are all in cases in which the major factors favoring wound infections are minimal.

From Tables VIII, IX, and X, therefore, the figures seem to indicate that in those wounds in which the major factors which would favor wound infections are minimal, these cases do better without the drugs. In the cases in which those factors are maximal the issue is not so clear but the weight of evidence is still not in favor of the sulfonamides.

The irrigation of wounds has been the subject of much discussion in the meetings of the committee. In the early part of the study it was the habit of some of the surgeons to have beside the operating table a stand to hold an irrigation can. Before débriding the wound,

TABLE XIII.—SOFT PART WOUNDS: INCIDENCE OF HEMOLYTIC STREPTOCOCCI AND COAGULASE POSITIVE STAPHYLOCOCCUS AUREUS IN THE DÉBRIDED TISSUE, THEIR PERSISTENCE IN LATER CULTURES AND THEIR LATER APPEARANCE IN CASES IN WHICH THEY WERE NOT ORIGINALLY FOUND WITH PARTICULAR REFERENCE TO DRUG TREATMENT

	Hemolytic streptococcus			Coagulase positive Staphylococcus aureus*		
	Débrided tissue	Persisting	New	Débrided tissue	Persisting	New
Total	55	11	18	74	16	51
Serious infection	9	4	6	7	3	14
Trivial infection	13	5	6	14	10	27
Controls: Total	14	0	4	17	1	9
Serious infection	0	0	3	2	1	2
Trivial infection	2	0	1	1	0	6
Sulfonamide cases: Total	41	11	14	57	15	42
Serious infection	9	4	3	5	2	12
Trivial infection	11	5	5	13	10	21

*This does not include other coagulase positive micrococci.

TABLE XIV.—SOFT PART WOUNDS: INCIDENCE OF PATHOGENIC AEROBIC GRAM-NEGATIVE BACILLI AND CLOSTRIDIUM WELCHII IN THE DÉBRIDED TISSUE, THEIR PERSISTENCE IN LATER CULTURES, AND THEIR LATER APPEARANCE IN CASES IN WHICH THEY WERE NOT ORIGINALLY FOUND, WITH PARTICULAR REFERENCE TO DRUG TREATMENT

	Pathogenic aerobic gram-negative bacilli			Clostridium welchii		
	Débrided tissue	Persisting	New	Débrided tissue	Persisting	New
Total	147	26	33	138	12	9
Serious infection	21	11	8	13	4	3
Trivial infection	20	8	19	19	3	4
Controls: Total	44	7	7	32	1	2
Serious infection	4	3	2	1	0	1
Trivial infection	3	1	5	7	1	1
Sulfonamide cases: Total	103	19	26	106	11	7
Serious infection	17	8	6	12	4	2
Trivial infection	17	7	14	12	2	3

it would frequently be subjected to extensive irrigation and in many cases this went on all during the operation. When the results of prolonged irrigation began to appear in the reports, this method was largely abandoned and the dry débridement, often with two sets of instruments, took its place. This is the more rational procedure for by it the great majority of the contaminating organisms are removed before there has been an opportunity to spread them around the wound. After débridement an irrigation of all loose particles which can be done in a few minutes may be of value. These cases have fallen into the short irrigation time group and cross tabulations seem to indicate that this factor *per se* is of some importance.

Many more similar cross tabulations have been made but they only confirm the results in the ones presented above which seem to illustrate the point clearly. No matter how we look at these results we cannot find any evidence to support the idea that the use of the sulfonamides has lowered the incidence of infection in the accidental soft part wounds which have been covered in this study.

The question has been asked whether the use of the sulfonamides will delay the onset of infection. It is of interest to note the day of the development of infection and correlate it with the method of drug therapy (see Table XI). When division is made into 5 day periods, it is seen that the largest proportion of the *serious* infections developed in the first 5 days while the largest percentage of the *trivial* infections developed in the second 5 days. It is seen that this was true both with the controls and with the patients treated with drugs. The figures for the first 5 days for both serious and trivial infections among the drug treated patients are slightly lower than in the controls suggesting that there was a slight delay in the onset of infection but the differences are not statistically significant because the series are small.

Of primary importance are, of course, the kind and degree of bacterial contamination. An attempt was made in one unit to make a quantitative determination of the number of organisms present but this was not found

TABLE XV.—SOFT PART WOUNDS: CROSS TABULATIONS BETWEEN BACTERIOLOGY AND COMPLETE CLOSURE OF WOUND WITH PARTICULAR REFERENCE TO DRUG TREATMENT

	Wound completely closed					
	Hemolytic streptococcus			Coagulase positive Staphylococcus aureus*		
	Débrided tissue	Persisting	New	Débrided tissue	Persisting	New
Total	46	7	12	58	12	36
Serious infection	7	2	5	5	3	10
Trivial infection	12	4	5	9	8	21
Controls: Total	13	0	4	15	1	9
Serious infection	0	0	3	2	1	2
Trivial infection	2	0	1	1	0	6
Sulfonamide cases: Total	33	7	8	43	11	27
Serious infection	7	2	2	3	2	8
Trivial infection	10	4	4	8	8	15

*This does not include other coagulase positive micrococci.

TABLE XVI.—SOFT PART WOUNDS: CROSS TABULATIONS BETWEEN BACTERIOLOGY AND COMPLETE CLOSURE OF WOUND WITH PARTICULAR REFERENCE TO DRUG TREATMENT

	Wound completely closed					
	Pathogenic aerobic gram-negative bacilli			Clostridium welchii		
	Débrided tissue	Persisting	New	Débrided tissue	Persisting	New
Total	121	16	22	106	6	7
Serious infection	13	6	6	7	2	2
Trivial infection	15	5	13	17	2	4
Controls: Total	40	6	7	29	1	2
Serious infection	3	2	2	0	0	1
Trivial infection	3	1	5	7	1	1
Sulfonamide cases: Total	74	10	15	69	5	5
Serious infection	9	4	4	7	2	1
Trivial infection	12	4	8	10	1	3

Note: Minor drug groups omitted.

feasible. It cannot be claimed that all of the qualitative analyses of the bacterial flora were complete or that the rarer species of organisms were always properly classified but the positive findings of the four main groups of pathogens seem reasonably accurate.

Table XII shows the frequency with which the four main groups of pathogens were found in the débrided tissue. It is seen at once that when these were found the incidence of infection ran higher than when the organisms were absent.

Tables XIII and XIV show not only the occurrence of these bacteria in the débrided tissue but also the number of times these four groups of organisms persisted and in how many cases these organisms were found later when they were not found originally, suggesting either a secondary contamination or the persistence of organisms originally present in such small numbers that they were missed in the first cultures. Furthermore, the presence, persistence, and new appearance of these organisms have all been correlated with drug treatment and the presence or absence of wound infection. It would appear from these tables that the organisms disappeared as readily from the wounds of the control cases as from those receiving primary drug and we have no indication whatsoever that the drugs primarily administered either locally or generally or combined were able to eliminate these organisms from these wounds. This is just as true of the hemolytic streptococcus and the Clostridium welchii which are ordinarily considered susceptible organisms as it is of the coagulase positive straphylococci and other micrococci and the pathogenic gram-negative aerobic bacilli, which are more resistant.

In considering the tables showing the incidence of the different organisms during the course of treatment, one is struck by three things. First, the small proportion of cases in which pathogenic organisms were found in the original cultures of the débrided tissue, which later developed clinical infection. This is particularly striking with the Clostridium welchii which was found in 138 cases while infection developed in only 32 and in only 2 of these was there clinical gas gangrene. Second, the rather small proportion of cases in which the organisms that were found originally, persisted in later cultures, for example 1/5 with the hemolytic streptococcus, 2/9 with the coagulase positive Staphylococcus aureus, 1/6 with the pathogenic gram-negative bacilli,

and 1/11 with the Clostridium welchii. These figures indicate not only the thoroughness of the removal of the organisms along with the débrided tissue but the ability of the body to take care of those organisms which were left behind. Third, although these organisms in some cases persisted in later cultures or appeared later for the first time there was not always evidence of clinical infection. This clearly indicates that the criteria of infection were not based on the presence of pathogenic organisms in the cultures but upon the clinical manifestations of their presence.

When the bacteriology is cross tabulated with the closure of the wound (see Tables XV and XVI) it is evident that in the closed wounds, pathogenic organisms were frequently found in later cultures even though they were not recovered from the débrided tissue. This suggests that they were there originally in too small numbers to be cultured and yet were able to gain a foothold in the tissues and grow out later. It is not likely, for example, that in many of the 12 closed cases in which the hemolytic streptococci appeared as new cultures, they entered the wound as secondary contaminants, coming from the respiratory passages of attending doctors and nurses, however prevalent that may be with regard to open wounds as suggested by Colbrook, Miles, Hare, and others. Furthermore both the persistence of pathogenic organisms in wounds which were closed and their appearance as new cultures not found originally occurred just about as frequently in the cases primarily treated with drugs as in the controls. Further studies with regard to the bacteriology will be reported later.

With regard to the blood levels and dosages of the sulfonamide drugs, some interesting points are brought out in Table XVII. There is a slight but not statistically significant higher incidence of infection when the blood level in the first 48 hours was below 7 milligrams per cent than when it was above that figure. A little wider difference is shown in the figures; for average blood levels during the next 8 days but this difference is almost entirely among the trivial infections. With doses of 9 grams or less in the first 48 hours, the figures are again slightly but not significantly higher than when the dose was above that figure; while the results during the next 8 days for those receiving less than 20 grams were actually a trifle lower than for those receiving more than that amount. In 508 cases of drug treated patients recording these data, there were 66 or 13 per cent which had some unfavorable renal reactions to the drugs and 35 or 6.9 per cent which had some other kind of reaction such as rash, fever, or fall in red or white blood cells.

TABLE XVII.—SOFT PART WOUNDS: DRUG DOSAGES AND BLOOD LEVELS WITH PARTICULAR REFERENCE TO THE INCIDENCE OF INFECTION

	Totals	Per cent infection		
		Serious	Trivial	Total
Free sulfa drug average blood levels: (primary sulfonamide only)				
48 hour level:				
Less than 7.0 gms.	357*	9.0	14.3	23.3
7.0 gms. or more	176*	6.2	12.5	18.7
Next 8 day level:				
Less than 7.0 gms.	385*	7.0	16.9	23.9
7.0 gms. or more	136*	8.8	8.1	16.9
Systemic sulfonamide: (primary sulfonamide only)				
In first 48 hours of drug therapy:				
Less than 9 gms.	250*	9.2	14.8	24.0
9 gms. or more	319*	6.6	12.5	19.1
In 3rd through 10th days of drug therapy:				
Less than 20 gms.	292*	6.2	14.0	20.2
20 gms. or more	258*	8.9	14.0	22.9

*These data not recorded on some of the summary sheets.

In spite of these far from satisfactory results with the sulfonamides in the prevention of infection in these accidental wounds there have only been 4 deaths from infection in all of these 926 cases. What does this signify? Perhaps the most plausible explanation is that the sulfonamides, while they have not been able to prevent or minimize local infections, have been able to prevent the general spread of infection to the rest of the body. Of these 4 fatal cases 3 were among the drug treated patients and one was among the controls but the drug treated patients all had serious injuries which may have contributed to the fatal outcome. When infection developed among the controls, the worst cases were

TABLE XVIII.—SOFT PART WOUNDS: SUMMARY OF 4 CASES, ALL WOUNDS CLOSED, IN WHICH DEATH FOLLOWED INFECTION. TOTAL CASE, 926

Case	Lesion	Operation	Primary drug	Secondary drug	Cause of death	Day of death	Principal organisms
Case 1	Avulsion of scalp	Débridement, closure with tension	None	Sulfadiazine	Meningitis	24th	Coagulose-positive staphylococcus Bacillus pyocyaneus
Case 2	Stab wound of chest, abdomen, diaphragm, and stomach	Débridement, closure without tension	Sulfanilamide locally, sulfadiazine generally	Sulfadiazine	Empyema	3rd	Hemolytic strept., Group F
Case 3	Gunshot wound of abdomen, perforation of ileum and cecum	Débridement, closure of perforations, closure of wound	Sulfanilamide in wound; sulfadiazine generally	Sulfadiazine	Peritonitis	3rd	B. coli, C. welchii, nonhemolytic strept.
Case 4	Gunshot wound of abdomen. Perforation of jejunum, rectum and bladder	Incomplete débridement, closure of perforations, partial closure with drainage	Sulfanilamide in wound. Sulfadiazine generally	Sulfadiazine	Peritonitis and pneumonia	5th	B. coli, green streptococcus

treated with sulfonamide as was done with the fatal case; so that we cannot say with certainty whether or not we would have had a higher incidence of sepsis and death among the controls if we had carried them through completely without drug. (See Table XVIII.)

For this reason we will have to fall back upon all of our past experience in order to say that we consider this mortality from infection of 0.43 per cent extremely low for these serious accidental wounds of the soft parts.

We wish to make clear that the results of this study should in no way be interpreted to mean that the sulfonamides haven't an important place in the treatment of infection. However, that rôle is not in the prevention of local infection in the wound but in the prevention of local infection from getting out of control by becoming general and causing sepsis and death. The problem of the development of local infection in these wounds still remains unsolved and it will not be solved until we can find some way for the sulfonamides or some other agent to be effective in wounds in the presence of damaged tissue.

COMPOUND FRACTURES

The problem of compound fractures is twofold: one, infection; the other, bone healing and subsequent bone and joint function. Our records contain many valuable data on the latter phase of the problem, but in this report we have considered this problem only from the point of view of infection. The end-result desired in compound fractures is a normally functioning member, with firm bony union and freely contracting muscle around the bone and freely moving joints on either end of the fractured bone. This end-result is materially altered or delayed by infection within or around the bone or by infection in the soft parts. Bone is less resistant to infection than are soft parts, and it is frequently cut off from its blood supply either as a loose fragment or as the exposed end of the shaft which has been stripped of its periosteum. Infection may develop at once, within the first few days after the injury, or start up with the first efforts to obtain full motion of the part, or lie dormant for months after the wound has apparently healed and suddenly or gradually develop after some trauma or some general lowering of resistance such as chilling or fatigue.

There were 674 compound fractures in this series with 14.1 per cent serious and 11.4 per cent trivial infections or a total of 25.5 per cent. Whereas there were twice as many trivial as serious soft part wound infections, the serious exceeded the trivial in compound fractures. This was to be expected because when bone becomes infected wound healing is usually delayed and hospitalization is usually prolonged. In many of the trivial cases only the soft parts were involved in the infection.

The compound fractures have been divided into major and minor. The former have included the large long bones of the upper and lower extremities in which the problem of bone overriding and angulation from muscle contraction and the necessity for either inter-

TABLE XIX.—BREAKDOWN OF THE CASES OF COMPOUND FRACTURES ACCORDING TO UNITS WITH PARTICULAR REGARD TO THE TYPE OF INJURY AND THE INCIDENCE OF INFECTION IN CASES OF DRUG TREATED PATIENTS AND IN CONTROLS

Hospital Units	Total cases	Major fractures			Minor fractures		
		Number of cases	Per cent infection		Number of cases	Per cent infection	
			Serious	Trivial		Serious	Trivial
Akron City	89	40	7.5	5.0	49	8.2	10.2
Charity, New Orleans	107	77	36.4	6.5	30	23.3	13.3
Cincinnati General	82	45	13.3	2.2	37	5.4	5.4
Detroit Receiving	173	97	9.3	17.5	76	10.5	19.7
Johns Hopkins	58	40	15.0	12.5	18	00.0	16.7
Massachusetts General	42	11	27.3	9.1	31	6.5	22.6
Presbyterian, N. Y.	123	104	14.4	9.6	19	10.5	00.0
Totals	674	414	16.9	9.9	260	9.6	13.8

Hospital units	Total cases	Sulfonamide cases			Controls		
		Number of cases	Per cent infection		Number of cases	Per cent infection	
			Serious	Trivial		Serious	Trivial
Akron City	89	75	8.0	9.3	14	7.1	00.0
Charity, New Orleans	107	104	32.7	7.7	3	33.3	33.3
Cincinnati General	82	68	11.8	4.4	14	00.0	00.0
Detroit Receiving	173	76	9.2	17.1	97	10.3	19.6
Johns Hopkins	58	58	10.3	13.8	0	00.0	00.0
Massachusetts General	42	39	10.3	20.5	3	33.3	00.0
Presbyterian, N.Y.	123	67	10.2	9.0	56	18.1	7.2
Totals	674	487	14.8	10.9	187	12.3	12.8

nal or external fixation, are of major importance. All of the others have been classified as minor. Table XIX divides the 674 compound fractures into major and minor according to their occurrence in the different hospital units and also divides them into drug treated cases and nondrug treated controls in each hospital unit, with the incidence of serious and trivial infection in all four groups. This table shows variations among the different units in the material available for study and in the methods of treatment, variations which are inherent in the set up of the different groups and yet which tend to balance one another. For

TABLE XX.—PERCENTAGE OF INFECTION IN COMPOUND FRACTURES OF THE DIFFERENT MAJOR LONG BONES

	Total cases	Per cent infection		
		Serious	Trivial	Total
Humerus	45	4.4	8.9	13.3
Radius	17	5.9	11.8	16.7
Ulna	28	7.1	3.6	10.7
Radius and ulna	40	10.0	7.5	17.5
Femur	30	23.3	10.0	33.3
Tibia	72	16.7	8.3	25.0
Fibula	11	9.1	00.0	9.1
Tibia and fibula	171	24.0	12.8	36.8
Totals	414	16.9	9.9	26.8

example, at Massachusetts General the minor fractures outnumbered the major 3 to 1, while at Presbyterian in New York there were 5 major to 1 minor, and at Charity in New Orleans the latter proportion was 2 to 1. Among the minor fractures at Presbyterian all of the infections were serious while at Johns Hopkins they were all trivial but both groups were small. In the major fractures, however, all units found the serious outnumbering the trivial. When grouped together it is seen that in the majority of the major fractures, infections were serious while among the minor fractures the reverse was true. Only four of the units used any appreciable number of controls and two of these only started to observe controls in the latter part of the study. In the whole group there were two and a half times as many drug treated cases as controls but neither of these two groups show any preponderance of those factors which favor infection. They, therefore, seem to be fairly comparable. This will be brought out clearer in the later tables. Table XX shows the incidence of infection for each of the major bones. It is seen that the total number of cases as well as the percentage of infection is much higher in the lower extremity than in the upper; both bones of the leg being the most common lesion and giving the highest percentage of both serious and trivial infections, with the femur coming a close second.

The principal factors concerned with the incidence of infection in compound fractures

TABLE XXI.—MAJOR FACTORS CONCERNED IN THE INCIDENCE OF INFECTION IN COMPOUND FRACTURES

	Totals	Per cent infection		
		Serious	Trivial	Total
Shock	176*	S.22.7	11.9	34.6
No shock	490*	S.11.9	11.4	23.3
Greater gross contamination	346	S.21.4	10.1	31.5
Lesser gross contamination	328	S. 6.4	12.8	19.2
Greater tissue damage	517	S.16.8	12.4	29.2
Lesser tissue damage	157	S. 5.1	8.3	13.9
Wound area >10 sq. in.	69*	S.27.6	14.5	42.1
Wound area <10 sq. in.	473*	S.10.8	10.6	21.4
Wound completely closed	412	S. 9.5	10.9	20.4
Wound partially closed	130	S.21.5	10.0	31.5
Wound left open	132	S.21.2	12.9	34.1
Plates	89	25.8	10.1	35.9
Plaster	346	16.8	10.1	26.9
Skeletal traction	116	21.8	14.8	36.6
Major fractures (large long bones of the extremities)	414	S.16.9	9.9	26.8
Minor fractures (all others)	260	S. 9.6	13.8	22.4
Irrigation >10 minutes	465*	14.4	10.3	24.7
Irrigation<10 minutes	207*	13.0	14.0	27.0
Operation after 3 hours	304*	15.8	12.5	28.3
Operation before 3 hours	362*	11.9	10.8	22.7
Incomplete débridement	208*	12.5	10.6	23.1
Complete débridement	451*	13.3	11.1	24.4

S., Statistically significant differences.
*Data missing on this point in a few of the cases.

TABLE XXII.—RESULTS OF WOUND CLOSURE WITH AND WITHOUT TENSION IN COMPOUND FRACTURES

	Wound closure		
	With tension	Without tension	Not recorded
Complete closure: Totals	67	265	80
Per cent serious infection	16.4	6.0	15.0
Per cent trivial infection	21.0	6.0	18.8
Partial closure: Totals	24	92	14
Per cent serious infection	25.0	21.8	14.3
Per cent trivial infection	20.8	9.8	7.1

TABLE XXIII.—INCIDENCE AND PERCENTAGE OF SERIOUS AND TRIVIAL INFECTIONS IN COMPOUND FRACTURES IN THE CONTROLS AND IN THE CASES WITH THE VARIOUS FORMS OF DRUG TREATMENT

	Cases	Number of infections			Per cent infection		
		Serious	Trivial	Total	Serious	Trivial	Total
Total number of cases	674	95	77	172	14.1	11.4	25.5
Neither general nor local sulfonamide	187	23	24	47	12.3	12.8	25.1
Total sulfonamide	487	72	53	125	14.8	10.9	25.7
General without local	104	13	7	20	12.5	6.7	19.2
General with local sulfanilamide and sulfadiazine	143	19	24	43	13.3	16.8	30.1
General with local sulfanilamide	209	36	13	49	17.2	6.2	23.4
Miscellaneous sulfonamide	31	4	9	13	12.9	29.0	41.9

are shown in Table XXI. Here it is seen that shock, greater gross contamination, greater tissue damage, and large-sized wounds give a significantly high percentage of serious infection. Other factors are apparently less important but all groups require cross tabulation to bring out their real appraisal. A surprising result is seen in the category of wound closure. The lowest group of serious infections is in the wounds which were completely closed while those partly closed or left open were both high. This finding has been consistent throughout the course of the study, and it seems to be statistically significant. It may be that cases which were closed completely were as a group less seriously injured, but another possible explanation for this is that when a compound fracture is left open or partly closed, the exposed bone, which is slow in being covered over with granulations, especially when there are separated fragments, is subject to prolonged exposure to the secondary contamination of organisms which are able to gain a foothold. As with soft part wounds, the element of tension in closure of the wound is of major importance (see Table XXII). The 265 cases in which closure was done without tension yielded only 6 per cent of serious infections and the same number of trivial infections, while those closed with tension had 16.4 per cent serious and 21 per cent trivial infections. One would have expected that when infection did take place in compound

TABLE XXIV.—COMPARABILITY OF THE DRUG TREATED CASES AND THE CONTROLS, IN COMPOUND FRACTURES, AS INDICATED BY THE PERCENTAGE OF CASES IN EACH OF THE TWO GROUPS OF SOME OF THE MAJOR FACTORS FAVORING WOUND INFECTION

	Controls—per cent	Sulfonamide cases—per cent
Greater gross contamination	50 3	52.0
Greater tissue damage	78.0	76.0
Area of wound over 10 sq. in.	9.1	10.7
Major bones involved	59.0	62.6
Wound left open or partly closed	40.8	38.0
Shock	22.2	27.8

TABLE XXV.—COMPOUND FRACTURES: COMPARISON OF THE DRUG TREATED CASES WITH THE CONTROLS WITHIN CERTAIN OF THE SUBGROUPS COVERING MAJOR FACTORS CONCERNED WITH WOUND INFECTION

	187 Controls				487 Sulfonamide cases			
	Total cases	Per cent infection			Total cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater gross contamination	94	18.1	9.6	27.7	252	22.6	10.3	32.9
Lesser gross contamination	93	6.5	16.2	22.7	235	6.4	11.5	17.9
Greater tissue damage	146	13.0	13.7	26.7	371	18.3	11.9	30.2
Lesser tissue damage	41	9.8	9.8	19.6	116	3.4	7.8	11.2
Large wound area	17*	23.5	28.4	51.9	52*	34.6	9.6	44.2
Smaller wound area S.	117*	5.9	6.5	12.4	356*	11.5	11.0	22.5
Major fractures (large long bone extremities)	110	11.8	10.0	21.8	304	18.8	9.9	28.7
Minor fractures (all others)	77	13.0	16.9	29.9	183	8.2	12.6	20.8
Wound left open	41	19.5	12.2	31.7	91	22.0	13.2	35.2
Wound partly closed	35	17.1	5.7	22.8	95	23.2	13.7	36.9
Wound completely closed	111	8.1	15.3	23.4	301	10.0	9.5	19.5

*Data incomplete.
S., Statistically significant differences.

fractures closed with tension that the serious infections would have outnumbered the trivial but such was not the case in this series. This relatively low incidence of serious infections in compound fractures closed with tension, cannot be attributed to the sulfonamides, for

TABLE XXVI.—COMPOUND FRACTURES: COMPARING THE DRUG TREATED CASES WITH THE CONTROLS WITHIN SUBGROUPS COMBINING TWO OF THE MAJOR FACTORS CONCERNED WITH WOUND INFECTION

	187 Controls				487 Sulfonamide cases			
	Total cases	Per cent infection			Total cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater contamination and greater tissue damage	86	16.3	9.3	25.6	224	24.0	11.2	35.2
Greater contamination and lesser tissue damage	8	37.5	12.5	50.0	28	10.7	3.6	14.3
Lesser contamination and greater tissue damage	60	8.3	20.0	28.3	147	9.5	12.9	22.4
Lesser contamination and lesser tissue damage	33	3.0	9.1	12.1	88	1.1	9.1	10.2
*Shock and greater tissue damage	37	13.5	13.5	27.0	121	27.2	12.4	39.6
*Shock and lesser tissue damage	5	20.0	00.0	20.0	13	00.0	23.1	23.1
*No shock and greater tissue damage	107	13.1	15.9	29.0	247	13.8	11.7	25.5
*No shock and lesser tissue damage	36	5.6	11.1	16.7	100	4.0	6.0	10.0

*No data regarding shock on 8 summary sheets.

in 34 such patients receiving both general and local sulfonamide there were 9 serious and 3 trivial infections while in 26 control cases there were only 1 serious and 8 trivial infections.

Table XXIII shows the compound fractures taken as a whole and divided according to the various forms of drug treatment. We find that the results with the three major methods of drug treatment do not differ significantly from one another nor from the controls, the serious infections among the drug treated cases being a little higher and the trivial a little lower than the controls.

Table XXIV lists the percentage of cases, within the control and drug treated groups, of the major factors favoring wound infection. None of these differences are statistically significant; this would seem to strengthen the belief that the two series are fairly comparable.

When comparisons are made between the controls and the drug treated cases within the

TABLE XXVII.—COMPOUND FRACTURES: COMPARING THE DRUG TREATED CASES WITH THE CONTROLS WITHIN SUBGROUPS COMBINING THREE OF THE MAJOR FACTORS CONCERNED WITH WOUND INFECTION

	Controls				Sulfonamide cases			
	Total cases	Per cent infection			Total cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater contamination and greater tissue damage and open or partly closed wound	S.38	23.6	7.9	31.5	94	36.2	12.8	49.0
Greater contamination and greater tissue damage and completely closed wound	48	10.4	10.4	20.8	130	15.4	10.0	25.4
Greater contamination and lesser tissue damage and open or partly closed wound	3	33.3	33.3	66.6	6	16.7	00.0	16.7
Greater contamination and lesser tissue damage and completely closed wound	5	40.0	00.0	40.0	22	9.1	4.5	13.6
Lesser contamination and greater tissue damage and open or partly closed wound	19	21.0	5.3	26.3	54	13.0	14.8	27.8
Lesser contamination and greater tissue damage and completely closed wound	40	2.5	27.5	30.0	94	7.5	11.7	19.2
Lesser contamination and lesser tissue damage and open or partly closed wound	16	00.0	12.5	12.5	31	00.0	16.1	16.1
Lesser contamination and lesser tissue damage and completely closed wound	18	5.6	5.6	11.2	56	1.8	5.4	7.2

S., Statistically significant differences.

framework of the different factors which play a rôle in wound infection (Table XXV) we find only one statistically significant difference and that favors the controls. What is more significant is the fact that in those groups in which the factors which favor wound infection are maximal the figures for the drug treated cases in all but 1 instance exceed the figures for the controls. In those groups in which the factors which favor wound infection are minimal, the controls are higher except in the category of small areas.

TABLE XXVIII.—COMPOUND FRACTURES: DAY OF ONSET OF SERIOUS AND TRIVIAL INFECTIONS CORRELATED WITH THE CASES RECEIVING DRUG TREATMENT AND WITH THE CONTROLS

	Number of cases	Not counted	Counted	Per cent of infections starting on days indicated			
				5 or less	6–10 days	11–15 days	over 15 days
Total infections	172						
Serious	95	9*	86	21.0	21.0	23.0	35.0
Trivial	77	15*	62	18.0	39.0	15.0	28.0
Controls: Total infection	47						
Serious	23	1*	22	9.0	27.0	27.0	37.0
Trivial	24	0*	24	25.0	50.0	17.0	8.0
Sulfonamide cases: Total infection	125						
Serious	72	8*	64	25.0	19.0	22.0	34.0
Trivial	53	15*	38	13.0	32.0	13.0	42.0

*Data regarding time of onset of infection are missing in these cases.

TABLE XXIX.—COMPOUND FRACTURES: INCIDENCE OF THE MAJOR PATHOGENIC ORGANISMS CULTURED FROM THE DÉBRIDED TISSUE AND THE PER CENT OF INFECTION IN THOSE CASES

	Totals	Per cent infection	
		Serious	Trivial
Hemolytic streptococcus: Found in cultures	50	S.24.0	S.26.0
Not found in cultures	624	13.3	10.3
Coagulase positive staphylococcus aureus*: Found in cultures	54	14.8	16.7
Not found in cultures	620	14.0	11.0
Pathogenic aerobic gram negative bacilli: Found in cultures	111	S.25.2	9.9
Not found in cultures	563	11.9	11.7
Clostridium welchii: Found in cultures	147	S.25.8	11.6
Not found in cultures	527	10.8	11.4
Combined pathogenic organisms: Hemolytic streptococcus and coagulase positive staphylococcus aureus	8	25.0	37.5
Hemolytic streptococcus and clostridium welchii	17	35.3	29.4
Coagulase positive staphylococcus aureus and clostridium welchii	29	27.6	27.6

*This does not include other coagulase positive micrococci.
S., Statistically significant differences.

When comparisons are made in Table XXVI between the controls and the drug treated

TABLE XXX.—COMPOUND FRACTURES: INCIDENCE OF HEMOLYTIC STREPTOCOCCI AND COAGULASE POSITIVE STAPHYLOCOCCUS AUREUS IN THE DÉBRIDED TISSUE, THEIR PERSISTENCE IN LATER CULTURES, AND THEIR LATER APPEARANCE IN CASES IN WHICH THEY WERE NOT ORIGINALLY FOUND WITH PARTICULAR REFERENCE TO DRUG TREATMENT

	Hemolytic streptococcus			Coagulase positive staphylococcus aureus*		
	Débrided tissue	Persisting	New	Débrided tissue	Persisting	New
Total	50	13	32	54	19	55
Serious infection	12	8	16	8	7	31
Trivial infection	13	2	8	9	7	11
Controls: Total	17	3	11	12	4	7
Serious infection	3	2	7	3	3	4
Trivial infection	5	0	3	1	1	0
Sulfonamide cases[1]: Total	31	9	20	40	15	48
Serious infection	8	5	9	5	4	27
Trivial infection	7	2	4	8	6	11

*Does not include other coagulase positive micrococci.
[1] Minor drug groups omitted.

TABLE XXXI.—COMPOUND FRACTURES: INCIDENCE OF PATHOGENIC AEROBIC GRAM NEGATIVE BACILLI AND CLOSTRIDIUM WELCHII IN THE DÉBRIDED TISSUE, THEIR PERSISTENCE IN LATER CULTURES, AND THEIR LATER APPEARANCE IN CASES IN WHICH THEY WERE NOT ORIGINALLY FOUND WITH PARTICULAR REFERENCE TO DRUG TREATMENT

	Pathogenic aerobic gram negative bacilli			Clostridium welchii		
	Débrided tissue	Persisting	New	Débrided tissue	Persisting	New
Total	111	20	55	147	21	14
Serious infection	28	13	17	38	12	5
Trivial infection	11	4	31	17	8	4
Controls: Total	26	6	21	47	6	5
Serious infection	3	0	5	15	5	1
Trivial infection	4	3	11	3	0	3
Sulfonamide cases: Total	78	11	28	92	13	8
Serious infection	23	11	10	20	7	4
Trivial infection	6	0	6	12	0	1

Note: Minor drug groups omitted.

cases by cross tabulations which combine two major factors concerned with wound infection, the numbers in each group become smaller and variations increase in number but it is to be noted that in the two categories in which those factors are maximal, the figures for the drug treated cases are higher than the control figures although the differences fall just short of statistical significance.

Table XXVII shows a further breakdown of the figures to combine three major factors. This table finds still more variations in the figures but the only significant difference is in the category in which all three factors are maximal and this difference favors the controls.

From these three tables XXV, XXVI, and XXVII, the evidence seems to be clear that in those situations in which local wound infection is favored to develop, the sulfonamides as they have been used in these civilian compound fractures under study have failed to demonstrate any definite prophylactic value.

It is of interest to note the difference in the time of the development of the infection in compound fractures as compared with soft part wounds and to correlate this time factor with the use of drugs. This is shown in Table XXVIII. It is seen that the onset of infection is frequently late, a large percentage of both serious and trivial infection appearing for the first time after 15 days. The question has been asked whether the sulfonamides delay the development of infection in these wounds or render them less serious, but this table gives no evidence to that effect. In the patients receiving drug treatment we find no lowering of serious infections as compared with the controls and if anything an earlier development.

Of major importance in the development of infection in compound fractures is of course the presence of pathogenic bacteria. Cultures of all of the débrided tissue reveal many species, and it will require special study to determine the significance of all of the organisms found. The tables shown herewith are concerned only with the four major pathogenic groups of organisms. Table XXIX gives the incidence of the hemolytic streptococci, the

TABLE XXXII.—COMPOUND FRACTURES: DEATHS FROM INFECTION—2 CASES IN A TOTAL OF 67

Case	Bones	Operation	Primary drug	Day of death	Principal organisms
Case 1	Tiba, fibula, ilium	Partial closure without tension. Plaster	Local sulfanilamide. General sulfadiazine	9th	Coag.-pos. Staphylococcus aureus, green streptococcus, Cl. bifermentans
Case 2	Femur, tibia and fibula	Partial closure with tension. Plate	Local sulfanilamide. General sulfadiazine	110th	Coag.-pos. Staphylococcus aureus, E. coli, B. proteus, B. pyocyaneus, Cl. sporogenes

coagulase positive Staphylococcus aureus, the pathogenic gram-negative aerobic bacilli, and the Clostridium welchii in the débrided tissue. The per cent of infection in the cases in which these were found is contrasted with the per cent of infection in the cases in which they were not found. It is seen that in all of these four groups the incidence of infection is higher where they were found. Except with the Staphylococcus aureus these differences are significant. This number would have been considerably augmented if other coagulase positive micrococci had been added. Combinations of these pathogens give a still higher incidence of infection but the number of cases in these categories is small.

Of greater interest still are Tables XXX and XXXI which show the number of cases in which the organisms, originally found in the débrided tissue, persisted in later cultures and the number of cases in which they appeared as new cultures not originally found. All of these data are correlated with the method of treatment in the three major categories of sulfonamide therapy and in the controls. In these tables it is seen that the wounds were generally more highly contaminated with pathogenic organisms than were the soft part wounds and a higher proportion persisted than in the wounds of the soft parts. A little over ¼ of the hemolytic streptococci, a little over 1/3 of the coagulase positive Staphylococcus aureus strains, 1/6 of the pathogenic aerobic gram-negative bacilli and 1/7 of the Clostridium welchii persisted. Thus it is evident that the débridement of the wound and the defense of the body rids the wound of the great majority of the contaminating organisms, but this holds true no more for the sulfonamide treated patients than for the controls. Furthermore the use of the sulfonamides did not prevent pathogenic organisms from appearing anew when they were not found in the débrided tissue, arising either from organisms present in such small numbers that they were not originally found or from organisms gaining a foothold as secondary contaminants. This holds true of the wounds which were closed as well as of those which were left open.

In spite of the unsatisfactory record of the sulfonamides as preventatives against local infection in these compound fractures, only 2 deaths from infection occurred (0.3 per cent) in the whole series. In both of the fatal cases the patients suffered injuries which were severe and played a part in the fatal outcome. Brief summaries of these cases are shown in Table XXXII. It is seen that both of these patients had local and general sulfonamide treatment and, although they died, they did not have septicemia. When infection developed in the control cases, sulfadiazine was generally administered and in these cases there were no deaths and none with septicemia. It seems fair to conclude therefore that while the sulfonamides failed to prevent local infection in compound fractures they have minimized the general spread of the local infection and may have reduced the number of deaths. But the problem of the prevention of local infection remains unsolved and will have to await the discovery of some new form of sulfonamide or some entirely new agent which will be bacteriostatic or bacteriocidal in the presence of damaged tissue.

BURNS

The problem of severe burns has five phases —shock, toxemia and nitrogen imbalance, infection, slough separation, and repair. While these five phases reach peaks of importance at different periods during the course of illness, they overlap to some extent. Infection has always been a serious problem in burns. Since the recent development of better understand-

ing and improved treatment for burn shock, infection has become of greater importance because of the large number of seriously burned individuals that have survived the shock phase. Infection is of importance prophylactically from the moment of injury until the whole area is again covered with skin. Burns differ from other wounds in two important respects: first, they are usually extensive but not deep, while other wounds are relatively deep but not extensive; second, it is not often possible or advisable to remove the dead tissue at the first surgical procedure as it is with other wounds. These two facts are important from the point of view of infection because the contamination with organisms is greater and impossible to remove and the medium which sustains their growth, that is, dead tissue, remains to favor their development. The bacteria causing infection in burns may be those residing normally in the hair follicles or sweat glands or those deposited on the surface subsequent to the burn. A superficial burn caused by low temperature applied for only a short duration may not kill all of the organisms in the hair follicles. A deep burn caused by a higher temperature applied for a longer time probably kills all of the bacteria in the skin in the central areas but at the margin there must always be areas where the burn becomes superficial and the organisms which are there, remain viable and capable of growth. In every case of burn there are three zones; one in which the tissue is killed directly by the heat, one in which it is injured but not immediately killed, and the third in which it is not injured at all. The thickness of these zones depends on the degree of heat and the duration of its application and the location on the body. Some of the injured tissue later dies and some recovers. A separation of the slough takes place between the living and the dead, and the time of its separation depends on a number of factors of which infection is one.

In this study the clinical observers have tried to maintain a uniform conception of the meaning of the terms, "second" or "third degree" burns and "serious" and "trivial" infections. In this study a second degree burn means one in which the superficial epithelium is injured to the extent of blistering and anything more severe than that short of a complete destruction of the deepest epithelial elements, so that restoration can take place from *residual* epithelium. A third degree burn has all of the epithelial elements destroyed so that epithelial repair has to take place from the margin or from skin grafts. It is obvious that the degree of any burn cannot be determined when the patient arrives at the hospital, or indeed until the repair has taken place or has failed to take place, spontaneously. Furthermore, there cannot be a sharp line between a deep second degree burn where repair takes place from scattered residual islands of epithelium and a superficial third degree burn. In this study burns that have had any amount of third degree areas have been placed in this category and an attempt has been made to estimate as nearly as possible the per cent of the body so involved. Similarly in those which have only second degree areas, the per cent of body surface has been approximately determined according to the scheme of Berkow.

With extensive surfaces involved, it is obvious that cultures taken from the surface will invariably reveal many kinds of organisms both at the time of admission to the hospital and all during the course of the illness, but, in this study, burns have only been called infected when in the judgment of all of those caring for the patient there was clinical evidence of a reaction of the body to the presence of organisms or their products. A serious infection has been distinguished from a trivial infection when there was clinical evidence of a general, as well as a local, reaction of the body to the infection or further destruction of tissue by the infection or a materially prolonged hospitalization due to the infection. In some cases it is most difficult to decide whether or not infection has occurred or whether it should be called serious or trivial because there is often some reaction of the body, both local and general, to the presence of dead tissue during the course of its separation from the body.

When this study was initiated there was a great diversity of opinion with regard to the best forms of treatment. These could be grouped in three main categories (1) tannic acid, (2) vaseline gauze with compression

TABLE XXXIII.—INCIDENCE OF INFECTION IN BURNS IN THE DIFFERENT HOSPITAL UNITS WITH SPECIAL REFERENCE TO THE DEGREE OF BURN AND SULFONAMIDE THERAPY

Hospital units	Total cases	Second degree			Third degree		
		Number of cases	Per cent infection		Number of cases	Per cent infection	
			Serious	Trivial		Serious	Trivial
Akron City	51	43	21.0	9.3	8	12.5	12.5
Charity, New Orleans	65	18	11.1	00.0	47	38.3	19.2
Cincinnati General	82	42	2.4	16.7	40	50.0	17.5
Cook County	52	20	10.0	15.0	32	21.9	40.6
Detroit Receiving	134	71	7.0	26.8	63	47.6	39.7
Henry Ford	63	39	2.6	15.4	24	29.2	58.3
Johns Hopkins	19	4	25.0	50.0	15	00.0	46.6
Massachusetts General	24*	11	18.2	27.3	13	76.9	7.7
Presbyterian, N. Y.	101	47	2.1	12.8	54	22.2	35.2
Totals	591	295	8.1	17.0	296	35.5	32.4

Hospital units	Total cases	Sulfonamide cases			Controls		
		Number of cases	Per cent infection		Number of cases	Per cent infection	
			Serious	Trivial		Serious	Trivial
Akron City	51	46	21.7	10.9	5	00.0	00.0
Charity, New Orleans	65	13	38.4	30.7	52	28.9	9.6
Cincinnati General	82	19	36.8	15.8	63	22.2	17.5
Cook County	52	26	19.2	38.5	26	15.4	23.1
Detroit Receiving	134	55	27.3	30.9	79	25.4	34.2
Henry Ford	63	22	13.6	40.8	41	12.2	26.8
Johns Hopkins	19	19	5.3	47.3	0	00.0	00.0
Massachusetts General	24*	22	54.5	13.6	2	00.0	50.0
Presbyterian, N. Y.	101	69	14.5	23.2	32	9.4	28.1
Totals	591	291	23.4	26.1	300	20.3	23.3

*This does not include the burns from the Cocoanut Grove disaster for which no opportunity was given for primary bacteriological study. Of the 26 burns of the skin who did not die of pulmonary injury in the first 4 days there were 14 serious infections and 1 trivial infection.

TABLE XXXIV.—MAJOR FACTORS IN THE INCIDENCE OF INFECTION FOLLOWING BURNS

	Totals	Per cent infection	
		Serious	Trivial
Second and third degree	296	S.35.5	S.32.4
Second degree only	295	S. 8.1	S.17.0
Greater gross contamiation	266	S.27.8	27.1
Lesser gross contamination	325	S.16.9	22.8
Greater tissue damage	300	S.27.2	S.28.5
Lesser tissue damage	201	S.11.4	S.17.4
Operation after 3 hours	149*	24.2	27.5
Operation before 3 hours	431*	20.7	24.2
Area over 10 per cent body surface	289	S.32.5	26.6
Area less than 10 per cent body surface	302	S.11.5	23.2
Shock	85*	S.36.5	25.9
No shock	493*	S.19.3	23.9

*Data missing in a few cases.
S., Statistically significant differences.

dressing, and (3) some form of sulfonamide. Even these did not satisfy all of the clinical observers and some desired to try out other frankly experimental methods. While it was recognized that if the number of categories were large, the number of cases in each category would be small, it was felt that during the first year at least, certain latitude should be given each unit to try out new methods with the proviso that at least two methods be consistently compared with one another in order to have some controls. In most of the units some sulfonamide method was compared with a nonsulfonamide method. Beside the variation in the local form of treatment, the opportunity was offered to either administer or withhold general drug therapy. It was recognized that the hemoconcentration and the fall in blood pressure, commonly occurring in severe burns, would increase the risk of toxic effects from kidney blockage with the sulfonamides. Therefore the general administration of the drugs was done cautiously, particularly when large areas were covered by drug-bearing local applications. All of the foregoing circumstances have diversified the methods of treatment in these cases, and yet it is believed that some order has been achieved out of chaos and some conclusions may properly be drawn from an assemblage and analysis of the data. Five hundred and ninety-one cases have been analyzed with serious infection observed in 21.8 per cent and trivial in 24.7 per cent or a total of 46.5 per cent infections.

Table XXXIII shows the breakdown according to hospital units with particular reference to the degree of the burn and the use of the sulfonamides. As with the soft part

TABLE XXXV.—COMPARISON OF SULFONAMIDE TREATED CASES AND NONDRUG TREATED CONTROLS IN 2ND AND 3RD DEGREE BURNS

	Second degree				Third degree			
	Number of cases	Per cent infection			Number of cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
No sulfonamide	158	7.0	17.1	24.1	142	35.2	30.3	65.5
Sulfonamide	137	9.5	16.8	26.3	154	35.7	34.4	70.1
General without local sulfonamide	27	11.1	18.5	29.6	56	35.7	35.7	71.4
Local without general sulfonamide	37	5.4	21.6	27.0	34	8.8	47.1	55.9
Both general and local sulfonamide	73	11.0	13.7	24.7	64	50.0	26.6	76.6

wounds and the compound fractures, this table reveals that there were differences between the units probably due not only to inherent differences in the available material for study but also due to variations in the interpretation of the definitions of second and third degree and serious and trivial infections mentioned above. For example it is seen that in the Akron and Henry Ford units, the burns were predominantly second degree while at Charity and Johns Hopkins they were predominantly third degree and in the other five units they were fairly equally divided. Furthermore the majority of the infections in the third degree burns were considered serious at Charity and Cincinnati and particularly at the Massachusetts General while all of the infections for third degree burns were considered trivial at Johns Hopkins. With regard to the distribution of drug treated and nondrug treated cases we find that four of the units had more sulfonamide cases than cases without sulfonamide, while in four the reverse is true and in one they are equally divided. This brings the totals approximately to equality. These differences or discrepancies do not invalidate the results for they tend to balance each other and they serve to emphasize the fact that in a study of this kind it is of the greatest importance to have it carried on in several different centers by several different groups of observers rather than to depend upon any one place to have available all types of cases or any one group of observers to make

TABLE XXXVI.—BURN CASES RECEIVING LOCAL AND NOT GENERAL SULFONAMIDE WERE GENERALLY LESS EXTENSIVE THAN THE OTHER SULFONAMIDE GROUPS, BUT THE DRUG TREATED CASES AS A WHOLE WERE SOMEWHAT MORE EXTENSIVE THAN THE CONTROLS

	Second degree		Third degree	
	Less than 10 per cent body surface	10 per cent or more body surface	Less than 10 per cent body surface	10 per cent or more body surface
No sulfonamide	117	41	121	21
Sulfonamide	97	40	122	32
General without local sulfonamide	14	13	45	11
Local without general sulfonamide	32	5	30	4
Both general and local sulfonamide	51	22	47	17

completely accurate and unbiased observations.

Table XXXIV shows that the main factor in the incidence of infection in burns is the depth or degree of the burn. The cases are almost equally divided between purely second degree and those having some element of third degree but the former group had only 8.1 per cent serious and 17.0 per cent trivial infections while the latter had 35.5 per cent serious and 32.4 per cent trivial infections. Other major factors, as with soft part wounds and compound fractures, are gross contamination, tissue damage, surface area, and shock. The factor of the time interval between injury and the first surgical treatments is not as important as it is in the other forms of injury studied. Approximately three quarters of the cases were treated within 3 hours.

When both the second and third degree groups are divided into those treated with some form of sulfonamide and those receiving no drug in any form, we find that there is approximately the same number of treated and nondrug treated cases in each group. Table XXXV shows no evidence, however, that the use of drugs has lowered the incidence of wound infection. In this table the sulfonamide treated cases have been divided into three groups—general alone, local alone, and

TABLE XXXVII.—COMPARISON OF BURN DRUG TREATED CASES AND CONTROLS WITHIN THE SUBGROUPS WHICH INCLUDE THE MAJOR FACTORS CONCERNED WITH WOUND INFECTION

	300 controls				291 sulfonamide cases			
	Total cases	Per cent infection			Total cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Second degree only	158	7.0	17.1	24.1	137	9.5	16.8	25.3
Second and third degree	142	35.2	30.3	65.5	154	35.7	34.4	70.1
Greater contamination	116	25.8	22.4	48.2	150	29.4	30.6	60.0
Lesser contamination	184	16.7	23.9	40.6	141	17.0	21.2	38.2
Greater tissue damage	192	28.6	26.0	54.6	198	25.6	30.6	56.2
Lesser tissue damage	108	5.6	18.5	24.1	93	18.3	16.2	34.5
*Operation after 3 hrs.	81	17.3	29.6	46.9	68	32.4	25.0	57.4
*Operation before 3 hrs.	209	20.6	22.0	42.6	222	20.7	26.1	46.8
Shock	24	50.0	20.8	70.8	61	31.2	27.9	59.1
No shock	270	17.4	23.3	40.7	223	21.5	24.7	46.2
Total burned area of body surface: Less than 5 per cent	75	2.7	12.0	14.7	66	6.1	15.2	21.3
5–9 per cent	74	16.2	33.8	50.0	69	21.5	31.9	53.4
10–19 per cent	93	22.6	24.7	47.3	87	26.4	29.9	56.3
20 per cent or over	58	38.0	24.2	62.2	69	45.0	24.6	69.6

*Data missing on 11 cases.

TABLE XXXVIII.—COMPARISON OF SULFONAMIDE TREATED BURN CASES AND NONDRUG TREATED CONTROLS IN THE SUBGROUPS OF THIRD DEGREE BURNS DIVIDED ACCORDING TO THE AREA INVOLVED WITHOUT REGARD TO THE EXTENT OF THE ASSOCIATED 2ND DEGREE AREAS

	Controls				Sulfonamide cases			
	Total cases	Per cent infection			Total cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
3rd degree burn area of body surface: Less than 5 per cent	89	18.0	34.8	52.8	89	31.5	36.0	67.5
5–9 per cent	32	56.3	25.0	81.3	33	42.4	36.4	78.8
10 per cent or over S.	21	76.2	19.0	95.2	32	40.6	28.1	68.7
Grafted cases: Less than 5 per cent	20	35.0	55.0	90.0	35	45.7	40.0	95.7
5–9 per cent	26	65.4	23.1	88.5	21	52.4	42.8	95.2
10 per cent or over	13	77.0	23.0	100.0	21	47.7	33.3	81.0

S., Statistically significant differences.

combined—and each one has been studied for the incidence of infection in second and third degree burns. We find that with one exception all of the drug treated groups have a higher incidence of infection than do the nondrug treated groups. That exception is in the smallest group of third degree burns, namely that which received "local without general sulfonamide." Here the per cent of serious infection is remarkably low. This low percentage is partly but not completely offset by a high per cent for trivial infections. When we look for an explanation of this apparent discrepancy, we find that this group was largely composed of burns of small area, in both the second and third degree groups, as is shown in Table XXXVI. This table also brings to light the fact that the controls had a lower percentage of extensive burns than the drug treated cases in both the second degree (26% to 29%) and in the third degree (15% to 21%) groups, but these differences are not statistically significant.

When the drug treated group and nondrug treated group are compared further within the subgroups pertaining to the major factors concerned with infection, the results are of interest. They appear in Table XXXVII. In each of the categories the numbers are about equally divided except for shock. Shock *per se* may be a factor favoring infection, but it has been thought that the *factors producing shock* are more important in that regard. In spite of this apparent weighting the sulfonamide group with more serious cases, the per cent of infection in the shocked cases seems to be considerably lower thus apparently favoring sulfonamide treatment but the difference is short of statistical significance, for the series is small. There seems to be also a preponderance of cases with greater contamination in the sulfonamide group but here the percentage of infection favors the controls and this difference is on the borderline of significance. In what is perhaps the most important category, namely

TABLE XXXIX.—BY CROSS TABULATIONS A COMPARISON OF DRUG TREATED BURN CASES AND CONTROLS WITHIN THE SUBGROUPS COMBINING TWO OF THE MAJOR FACTORS CONCERNED WITH THE DEVELOPMENT OF INFECTION IN BURNS

	Controls				Sulfonamide cases			
	Total cases	Per cent infection			Total cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Greater contamination and greater tissue damage	95	30.5	26.4	56.9	124	26.6	34.7	61.3
Greater contamination and lesser tissue damage	21	4.8	4.8	9.6	26	42.3	11.5	53.8
Lesser contamination and greater tissue damage	97	26.8	25.8	52.6	74	24.3	24.3	48.6
Lesser contamination and lesser tissue damage	87	5.8	21.8	27.6	67	8.9	17.9	26.8
Greater contamination and shock	15	46.7	23.9	70.6	42	31.0	31.0	62.0
Greater contamination and no shock	99	22.2	22.2	44.4	103	29.1	29.1	58.2
Lesser contamination and shock	9	55.5	22.2	77.7	19	31.6	21.0	52.6
Lesser contamination and no shock	171	14.6	24.0	38.6	120	15.0	20.8	35.8

"greater tissue damage," the numbers are almost equally divided both for the number of cases and for the percentage of infections.

The figures for area are of considerable interest. Here the total areas are given, and in each group the figures for the drug treated cases are higher than for the controls. These differences would not of themselves be significant except that they all point in the same direction which is in favor of the controls. If we combine the factors of extent and depth in the third degree burns, we find that in the smaller area burns the number of drug treated and nondrug treated cases is almost identical both in the numbers of cases and the per cent of infections, while in the most extensive group there were more patients who received the drug and yet they had a lower percentage of infections. If, however, we count only those patients who lived long enough to have grafting done the difference is not so great and falls short of statistical significance. In all of these comparisons, therefore, we can find no clear cut

TABLE XL.—PERCENTAGE OF INFECTION ASSOCIATED WITH DIFFERENT FORMS OF LOCAL TREATMENT IN THE NONDRUG TREATED BURN CASES

	Second degree				Third degree			
	Number of cases	Percent infection			Number of cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Vaseline with pressure	70	4.3	11.4	15.7	47	27.7	42.5	70.2
Boric acid with pressure	9	11.1	11.1	22.2	2	00.0	00.0	00.0
Lanolin with pressure	11	00.0	27.3	27.3	10	50.0	10.0	60.0
Saline with pressure	15	6.7	00.0	6.7	35	37.2	17.2	54.4
Zinc peroxide with pressure	21	9.5	33.3	42.8	23	34.8	30.4	65.2
Tannic acid	7	14.3	28.6	42.9	9	44.4	55.6	100.0
Quibracho tannin	4	50.0	25.0	75.0	5	60.0	20.0	80.0
Miscellaneous	21	4.8	23.8	28.6	11	36.4	27.3	63.7
Totals	158	7.0	17.1	24.1	142	35.2	30.3	65.5

evidence of the value of the sulfonamides in the prevention of infection in burns except possibly in the most seriously and extensively injured group. Let us turn, therefore to a further breakdown of the figures. When two of the factors are combined, as in Table XXXIX, there are no differences of statistical significance except for one small group which favors the controls. In other categories there is little to choose between the two groups.

Tables XL, XLI, XLII, and XLIII give the results for the various forms of treatment. As has been stated, the local treatment in these cases has been quite diverse in an effort to discover some outstanding method that would minimize infections. Table XXXV indicates that about one half of the cases had no sulfonamide drug treatment of any kind; one half of the remainder received sulfonamide both locally and generally while the other half was divided almost equally between those receiving drug locally but not generally and those receiving it generally but not locally. Each of these groups has been broken down into various categories of local treatment and within these groups the second and third degree burns have been compared. With both the drug treated and nondrug treated cases two principles of dressing have been used; one, the com-

TABLE XLI.—PERCENTAGE OF INFECTION ASSOCIATED WITH DIFFERENT FORMS OF LOCAL TREATMENT IN THE BURN CASES RECEIVING SYSTEMIC BUT NO LOCAL SULFONAMIDE

	Second degree				Third degree			
	Number of cases	Per cent infection			Number of cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Vaseline with pressure	7	14.3	28.6	42.9	17	29.4	41.2	70.6
Boric acid with pressure	4	00.0	00.0	00.0	7	42.9	28.6	71.5
Lanolin with pressure	3	00.0	00.0	00.0	8	62.5	12.5	75.0
Saline with pressure	0	00.0	00.0	00.0	9	33.3	44.4	77.7
Zinc peroxide with pressure	4	00.0	25.0	25.0	10	20.0	40.0	60.0
Tannic acid	5	40.0	20.0	60.0	0	00.0	00.0	00.0
Miscellaneous	4	00.0	25.0	25.0	5	40.0	40.0	80.0
Totals	27	11.1	18.5	29.6	56	35.7	35.7	71.4

TABLE XLII.—PERCENTAGE OF INFECTION ASSOCIATED WITH DIFFERENT FORMS OF LOCAL TREATMENT IN THE BURN CASES RECEIVING LOCAL BUT NO SYSTEMIC SULFONAMIDE

	Second degree				Third degree			
	Number of cases	Per cent infection			Number of cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Sulfadiazine ointment	19	00.0	36.8	36.8	9	00.0	66.7	66.7
Sulfadiazine spray	4	00.0	00.0	00.0	9	11.1	44.4	55.5
Sulfathiazole ointment	4	00.0	00.0	00.0	3	00.0	00.0	00.0
Sulfonamide film	3	00.0	00.0	00.0	5	00.0	40.0	40.0
Sulfonamide powder	0	00.0	00.0	00.0	4	50.0	25.0	75.0
Tannic acid and sulfonamide	1	00.0	00.0	00.0	4	00.0	75.0	75.0
Miscellaneous	6	33.3	16.7	50.0	0	00.0	00.0	00.0
Totals	37	5.4	21.6	27.0	34	8.8	47.1	55.9

pression dressing over a powder or over a nonadherent ointment and the other an eschar forming preparation either tanning the skin or covering it with an adherent film and leaving it exposed. In some cases a preformed film was used together with a compression dressing.

In Table XL the nondrug treated cases are shown. The large number of categories has reduced the figures for each form of treatment

TABLE XLIII.—PERCENTAGE OF INFECTION ASSOCIATED WITH DIFFERENT FORMS OF LOCAL TREATMENT IN THE BURN CASES RECEIVING BOTH LOCAL AND GENERAL SULFONAMIDE

	Second degree				Third degree			
	Number of cases	Per cent infection			Number of cases	Per cent infection		
		Serious	Trivial	Total		Serious	Trivial	Total
Sulfadiazine ointment	14	00.0	21.4	21.4	25	48.0	20.0	68.0
Sulfadiazine spray	15	00.0	20.0	20.0	5	20.0	60.0	80.0
Sulfathiazole ointment	8	00.0	12.5	12.5	11	27.3	45.5	72.8
Sulfonamide film	5	40.0	40.0	80.0	4	50.0	00.0	50.0
Sulfonamide powder	17	35.3	00.0	35.3	4	100.0	00.0	100.0
Tannic acid and sulfonamide	10	00.0	10.0	10.0	11	63.7	27.3	91.0
Miscellaneous	4	00.0	00.0	00.0	4	75.0	25.0	100.0
Totals	73	11.0	13.7	24.7	64	50.0	26.6	76.6

with wide variations in percentages for infection. However, a few general statements seem warranted. It is clear that there was a higher incidence of infection in third degree than in second degree burns for almost all forms of treatment. The chief consideration should be given to the third degree column. It is evident that the tannic acid cases did badly. This was so apparent in all of the units in the earlier reports that the method was discarded fairly early in the course of the study. For that reason the number of cases was small for both forms of tannic acid. Early favorable observations with boric acid ointment recommended it to the staff of the Massachusetts General Hospital when the Cocoanut Grove disaster came upon them. The facilities of the laboratory were swamped and it was not possible for them to make any primary bacteriological cultures. They have therefore not been included in this final summary. Six of the 39 cases had no surface burns; 6 died on the second to fourth day from inhalation burns, 1 was transferred on the second day. We have, however, the records of 26 of these cases and know that the per cent of infections was 54 per cent serious and 3.8 per cent trivial. Among the other methods of local treatment none is outstanding, and the percentage differences are not significant.

TABLE XLIV.—TIME OF ONSET OF THE INFECTION AS CORRELATED WITH THE USE OR NONUSE OF SULFONAMIDE TREATMENT IN 232 OF THE 275 CASES OF INFECTION FOLLOWING BURNS

	Number of cases	Not counted	Counted	Per cent of infections occurring in each 5 day period			
				5 days or less	6–10 days	11–15 days	more than 15 days
Total infections	275						
Serious	129	22*	107	25.2	39.3	15.9	19.6
Trivial	146	21*	125	28.8	28.8	31.2	11.2
Controls: Total infection	131						
Serious	61	5*	56	23.2	46.4	8.9	21.5
Trivial	70	9*	61	27.9	27.9	36.0	8.2
Sulfonamide cases: Total infection	144						
Serious	68	17*	51	27.5	31.4	23.5	17.6
Trivial	76	12*	64	29.7	29.7	26.6	14.0

*Data regarding time of onset of infection are missing in these cases.

TABLE XLV.—INCIDENCE OF CERTAIN OF THE PATHOGENIC BACTERIA IN THE DEBRIDED TISSUE IN BURNS, THEIR PERSISTENCE IN THESE CASES AND THEIR APPEARANCE IN OTHER CASES IN WHICH THEY WERE NOT ORIGINALLY FOUND, WITH PARTICULAR REFERENCE TO SULFONAMIDE TREATMENT AND THE DEGREE OF THE BURN

	Second degree			Third degree		
	Debrided tissue	Persisting	New	Debrided tissue	Persisting	New
Hemolytic streptococcus No sulfonamide	15	3	6	16	5	25
Sulfonamide	21	2	3	25	7	22
Coagulase positive Staphylococcus aureus No sulfonamide	13	6	8	22	13	16
Sulfonamide	27	9	11	20	11	36
Pathogenic aerobic gram-negative bacilli No sulfonamide	32	5	10	33	11	45
Sulfonamide	33	4	10	45	21	41
Clostridium welchii No sulfonamide	40	6	1	40	5	1
Sulfonamide	46	1	1	49	5	4

Table XLI shows the same types of local treatment as in Table XL, combined with the systemic administration of sulfonamide—usually sulfadiazine. These figures do not materially differ from those without the drug but in all but one category they are higher rather than lower for the third degree burns.

In Table XLII the cases are grouped according to the different local sulfonamide treatments, none of these having received systemic sulfonamide. Table XLIII includes those cases which had both systemic and local sulfonamide. The figures for the combined treatment are no better than in those patients which received no general drug. No one form of treatment is outstandingly good. The tannic acid combinations and the powdered sulfonamide cases may be said to be inferior, the latter group showing a particularly high percentage of serious infections. The sulfonamide film cases yield the lowest figures for the third degree burns, but the figure is high in the second degree group and the total numbers are small. Further observations with this form of treatment are needed.

From these four tables no one method of local treatment stands out above the others but, taken as a whole, the compression dressing method has been found to be superior to the eschar forming treatments.

The day of onset of infection is of interest as is shown in Table XLIV. The time of onset was not noted in some of the early cases but we have data of this kind for 232 of the 275 cases which developed infection. These have been divided into those receiving sulfonamide and those without sulfonamide, and each of these main groups has been subdivided into 5 day units. It is seen from this table that in the whole series the peak of the serious cases developed in the second 5 day period while in the trivial cases the onset was fairly evenly distributed through the first 15 days. There is no indication from the figures on the table that infection in the sulfonamide treated patients was delayed by this treatment or that the infection was less serious than in the nondrug treated cases.

The bacteriology of burns covers a wide range if a careful analysis is made of the bacterial flora present in the loose skin removed from the burned area. Swab cultures are

TABLE XLVI.—DEATHS FROM INFECTIONS, 3 CASES IN A TOTAL OF 591 CASES

Cases	Degree	Region	Per cent of body surface	Local treatment	Primary general drug	Secondary general drug	Day of death	Principle organisms
Case 1	2nd and 3rd degree	Face, trunk, both arms and hands, right leg	60–70	Equal parts powdered sulfanilamide and sulfadiazine	Sulfadiazine	Sulfadiazine	5th	Coag.-pos. staph., nonhemolytic strept., B. pyocyaneus, B. proteus
Case 2	2nd and 3rd	Face, trunk and all limbs	60–70	Fibrinogen, thrombin, sulfadiazine	Sulfadiazine	Sulfadiazine	28th	Coag.-pos. staph.; hemolytic strept., group D; B. pyocyaneus; E. coli
Case 3	2nd and 3rd	Face, trunk, upper extremities and thighs	40–50	Tannic acid before admission. Vaseline with pressure after admission	None	Penicillin	24th	Coag.-pos. staph. (septicemia); hemolytic strept., group G; B. melaninogenicum

entirely inadequate and even the cultures of all of the tissue removed cannot reveal with certainty all of the organisms present in any given case. It will take some time to analyze the data especially with regard to the results with combination of organisms. For this report, interest has been centered around the well known pathogenic organisms, namely the hemolytic streptococcus, the coagulase positive staphylococci, the gram-negative bacilli of the eschericha, aerobacter, typhoid-dysentery, pyocyaneus and proteus groups, the Clostridium welchii, the anaerobic streptococci, and other pathogenic anaerobes.

We have been particularly interested not only in the incidence of these organisms in the débrided tissue but the persistence of these organisms in the cases during the course of treatment and their later appearance as apparently new cultures in cases in which they were not originally found. These figures, which appear in Table XLV, are broken down to show the influence of the sulfonamides on this persistence and new development.

One is struck by the large number of cases in which these organisms are originally found, which failed to develop infection and also by the comparatively large number of cases in which they appeared as new cultures. It is equally obvious from these charts that the primary use of sulfonamides has not been associated with the more thorough elimination of these organisms than in the control cases nor have they prevented the establishment of the organisms in the wound.

During the first year it was particularly evident that the anaerobes were more easily eliminated from these burns than were the aerobes. Apparently the surface of dead skin does not offer the same favorable environment for growth and invasion as the muscular layers. It was therefore decided at the end of the first year to omit the anaerobic cultures on burns unless infection developed. No anaerobic cultures were taken in 204 of these burns. The incidence of anaerobes in the débrided tissue is therefore based on 287 cases, anaerobes being found in 261.

In spite of the apparently questionable value of the sulfonamides in the prevention of local infection in burns there were only 3 deaths from infection in the whole series—0.5 per cent. Brief abstracts of these cases are shown in Table XLVI. These were all second and third degree burns with 50 per cent or more of the body surface involved. Two were primarily treated with general sulfadiazine and one of these with local sulfonamide as well, neither developed septicemia. The third had no general drug. Tannic acid had been used before admission but after admission the local treatment was changed to vaseline gauze and compression. Staphylococcus aureus septicemia developed in the 5th day and failed to respond to penicillin although death did not occur until the 24th day. This may be considered a low mortality from infection in burns. When the controls became seriously infected, sulfonamides were often used systemically, and we therefore have no control series carried through the whole course of treatment to compare with the mortality figures with the sulfonamide treated patients.

The sulfonamides have apparently been useful in treating cases of infection by reducing its spread from the original site. This has ap-

parently been done successfully in cases that were not originally treated with the drug. There is no indication from this study that these drugs should be used as prophylactic agents in cases of burns.

GENERAL SUMMARY

A study and an appraisal have been made of the use of sulfonamides as preventatives against wound infection in civilian accidental wounds of the soft parts, compound fractures, and burns in order that there might be a rational basis established for their use in the prevention of infection in war wounds.

For this purpose nine units studied clinical cases in various parts of the country. A uniform method of gathering data has been used in an effort to record in every case the presence or absence of factors which might play a rôle in favoring or minimizing wound infection in the individual case. All of the cases have had the best possible surgical care of which the individual units have been capable. This has generally consisted in prompt operation and the removal of all of the devitalized tissue except in burns. Bacteriological studies have been made of the tissue removed from the wound and of material from the wound itself, when indicated during the course of treatment,—so that it might be known with what bacterial contamination the various forms of treatment had to deal and under what conditions each treatment succeeded in preventing infection and in what conditions it failed to do so.

The results in cases treated with sulfonamides have been compared with the results in nondrug treated controls. Although the number of controls in the different units has varied, the importance of maintaining the controls as a strictly parallel series has been constantly kept in mind. One can be certain that there was no conscious selection of cases which might prejudice the results either in the controls or in drug treated cases. All of the responsible investigators and the clinical directors of the different units are agreed that the controls reported here offer a fair basis for comparison. Furthermore, an analysis of the factors present, both in the drug treated cases and in the controls, seems to indicate that this is true within the limits of control discussed.

The data from 2,191 cases have been studied and analyzed with the aid of Dr. John Fertig, professor of biostatistics of Columbia University. Of these there were 926 soft part wounds, 674 compound fractures, and 591 burns.

The chief factors concerned with the development of infection in compound fractures and soft part wounds have been found to be (1) the degree and extent of tissue damage, (2) the degree of gross contamination by dirt and other foreign bodies, (3) the duration of time between the injury and the surgical care, (4) the nature of the bacterial flora in the wound, and (5) the care and thoroughness with which the devitalized tissues, foreign bodies, and gross contamination are removed from the wound. In burns the first four of these apply but the most important factor is the extent of the deep burn.

The use of the sulfonamides as employed in these cases either systemically alone or locally alone, or combined, has not materially reduced the incidence or the severity of local infections in the wounds or burns nor have they delayed the development of infection nor have they eliminated the pathogenic organisms from the wounds. It seems likely, however, that they have minimized the spread of the local infection into the general circulation and have therefore cut down the incidence of septicemia and death. This has been accomplished by systemic drug therapy when infection developed in the controls, as readily as when the drugs have been used either locally or generally as prophylactic agents and employing them only as therapeutic agents after infection has developed. Omitting the routine early use of these drugs would avoid a great waste of material and many toxic reactions. However, if this is done in a rush of military hospital work, the onset of infection might be overlooked and septicemia might be established before the drugs could be effectively administered.

It was hoped that it would be possible to demonstrate by statistical methods that the sulfonamides were capable of materially reducing the incidence of infection in wounds treated under the conditions to be found in a number of good civilian hospitals. In fact, it

was not beyond the hope of certain individuals that they would be able to do this in spite of certain compromises with surgical principles such as incomplete removal of devitalized tissue and gross contamination—such as might be necessary under the stress of military conditions or when careless ward dressings are done without due regard to the possibilities of secondary wound contamination from the hands or from the nose and throats of the attendants. But such was not the case. Our carefully analyzed figures show that when the local conditions favored infection, the controls on the whole did better than the drug treated cases. These are precisely the conditions in which it was hoped that the drugs might be of value. This tends to lend weight to the belief that the presence of devitalized or damaged tissue in some way inhibits the bacteriostatic action of the sulfonamides.

The problem of secondary contamination has not been thoroughly explored although data on some of the points involved are available on the summary sheets and will be included in the later bacteriological report. Most of the units took special precautions to avoid secondary contamination of the wounds as far as local conditions permitted. The development of hemolytic streptococcus infections in closed wounds when that organism was not found in the débrided tissue strongly suggests that many of the organisms which develop a wound infection are among the primary contaminants but present in such small numbers that they are not recovered from the primary cultures.[1]

All of the results seem to indicate that the main dependence of the surgeon in the prevention of infection both in civilian accidental wounds, and in the war wounds must be placed upon the well known principles of the surgical care of contaminated wounds,—namely the removal of the devitalized tissue and the contamination and the rapid restoration of the normal physiology of the part involved. The use of the sulfonamides can in no measure make up for this.

The results of this study have surprised many people and are presented with the keen disappointment of all of those who have worked on the problem, for all hoped that something would be found which would prevent infections in these wounds. However, the facts must be faced, the problems which they present must be understood and an attempt must be made to solve them; because in war wounds, local infection, even if it does not result in death, causes prolonged hospitalization and either temporary or permanent disability or deformity, frequently with loss of limb. Effort must be made in the following directions: (1) to find out what interferes with the bacteriostatic action of sulfonamides in the wound or on the surface of a burn, (2) to find some way to inactivate the inhibitors, (3) to find some form of sulfonamide which will not be inhibited in the wound, (4) to find some other agent which will eliminate the bacteria from the wound or nullify their action without injury to the wound itself.

Certain of the units are pursuing these problems with particular reference to the prophylactic value of the microcrystals of sulfathiazole and of penicillin. Further studies must be made on other promising agents, such as the proflavines, the oxyquinolines, the carboxymethoxylamines, other oxidizing agents and radiotherapy.

[1]The Lancefield grouping of the hemolytic streptococci found in these cases will be the subject of a separate report.

THE ABSORPTION OF SULFONAMIDES FROM THE BURN SURFACE

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G. WATSON JAMES, III, M.D., Richmond, Virginia

FOLLOWING the rather extensive local use of sulfanilamide to prevent infection in wounds, it was only natural that, since infection is one of the chief problems in severe burns, sulfanilamide should have been used locally in burns. Unfortunately, the clinical demonstration by Hooker and Lam that this practice may be associated with extremely high blood levels of sulfanilamide due to the ready absorption of sulfanilamide powder from the burned surface has not deterred some persons from advocating "sulfanilamide ointment" for the treatment of burns, without specifying the degree of absorption to be expected or the type of ointment to be employed.

The study reported here has been concerned with an attempt to ascertain the influence of the ointment base on the relative absorption of sulfonamides from the burned surface, in patients with severe burns. In commercial pharmaceutical practice, ointment bases are essentially of two contrasting emulsion types, namely: (1) oil in water, in which the water phase is external; and (2) water in oil, in which the water phase is internal. Since sulfanilamide is practically insoluble in oil (7 to 8 mgm. per 100 c.c.) but relatively soluble in water (1500 mgm. per 100 c.c.) (4), it will be immediately surmised that there is a marked preferential solution of sulfanilamide in the water phase of the emulsion. Thus, great differences are likely to be found in the relative absorption of the drug from the burned surface, depending on which phase, water or oil, is continuous with the absorbing burned surface. That such is actually the case in clinical practice will be demonstrated.

The sulfonamide ointments studied were of the following compositions:

Oil in water emulsion—("water dispersible base")

	Per cent
Mineral oil	17
White wax	7
Water	61
Emulsifying agents	5
Sulfanilamide	5
Sulfathiazole	5

From the Department of Surgery, Medical College of Virginia.

This study has been carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and The Medical College of Virginia.

Water in oil emulsion—("oil base")

	Per cent
White wax	5
Petrolatum	47
Paraffin	10
Water	23
Emulsifying agents	5
Sulfanilamide	5
Sulfathiazole	5
MCV[1] ointment	
Peanut oil	12
Lanolin	41
Rose water ointment	41
Sulfanilamide (100 mesh powder)	6

[1]Medical College of Virginia.

It will be noted that the percentages of sulfanilamide and sulfathiazole are the same in each ointment type; the formula for our own oil base ointment is shown because of the many requests we have had for this information; the only essential and important pharmaceutical differences in the two ointments employed in this study are that they are two distinctly different types of emulsion. We believe that the two types are characteristic of the average ointments supplied by pharmaceutical houses or hospital drug rooms.

CLINICAL OBSERVATIONS

All burned patients were treated in essentially the same manner. There were 15 burn patients on whom the oil-in-water (water dispersible base) emulsion was used, and 12 on whom the water-in-oil (oil base) emulsion was used.

The same regimen of burn therapy was employed in each group. The burned areas were gently cleaned with soap and water, the easily removed skin excised, the ointment spread thickly over the burned area, and occlusive pressure dressings applied. Plasma and fluids were given as the patient's needs were indicated in each case by hematocrit studies every 6 hours. A blood sulfanilamide was determined on each hematocrit sample by the Marshall colorimetric method. (No attempt was made to differentiate between blood sulfanilamide and sulfathiazole.)

A. Water dispersible base. Four representative patients' protocols and sulfonamide absorption charts are shown.

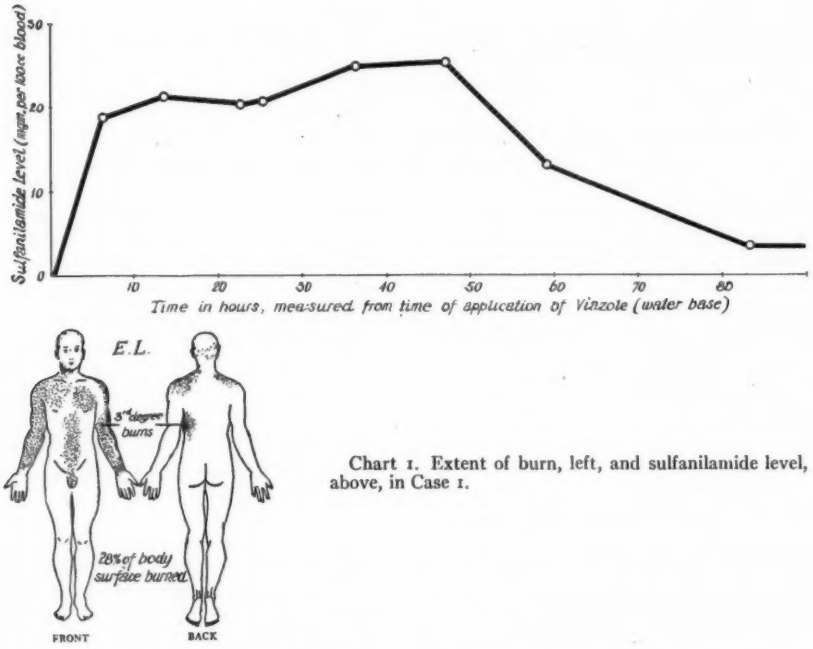


Chart 1. Extent of burn, left, and sulfanilamide level, above, in Case 1.

CASE 1. E. L. (Chart 1.) A 2 year old child received deep burns from boiling water on the anterior chest, face, arms, and hands. Water dispersible base on fine mesh gauze was placed on burned areas; 200 cubic centimeters of plasma was given. Patient did well, but during first 24 hours respiratory rate had risen to 60, pulse rate 160, and temperature was 97 degrees. The patient presented many of the signs of extreme peripheral vascular collapse. Blood studies showed nonprotein nitrogen of 90, sulfonamide level 20.4 milligrams per cent. Urine examination showed: albumen, 2 plus; many sulfathiazole crystals. The clinical picture was one of sulfonamide intoxication. The water dispersible base was removed from the burned area and replaced with vaseline guaze. Although clinical improvement was apparent by the next day, the sulfonamide blood level remained high until about the 48th hour. The urine contained sulfathiazole crystals until after the 3d day. When the dressings were removed on the 10th day, there was no evidence of surgical infection, but it was apparent that large areas of the burn would require skin grafting. The patient was removed from the hospital against advice.

CASE 2. B. M. (Chart 2.) A 4 year old child was burned on the entire trunk, chest, abdomen, both upper extremities, neck and face from burning clothes. Patient was given 250 cubic centimeters of plasma, then dressings were made with water dispersible base ointment. Despite extensive deep burns, secondary shock was rather easily controlled in this patient by 250 cubic centimeters of plasma every 12th hour until the 72d hour, when whole blood transfusions were started. Chart 2 illustrates the absorption of sulfonamides from the burned surfaces of this child. Although the blood levels reached 28 milligrams per cent, there was no clinical evidence of sulfonamide toxicity, nor did the urine contain any sulfathiazole crystals.

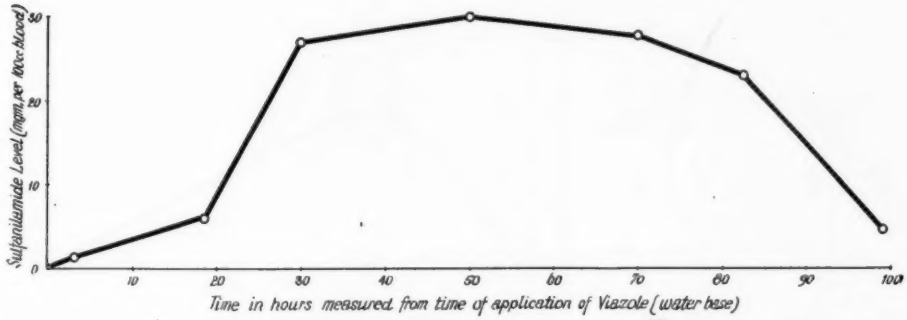
The removal of necrotic skin proceeded rapidly in this child so that in 26 days pinch grafting could be started. The hospital stay was long (7 months); 9 operations were performed, including 2 dermatome grafts.

CASE 3. Q. B. (Chart 3.) A 22 year old male was burned by clothes catching on fire. After cleansing, the burned areas were covered with water dispersible base ointment and pressure dressings. Plasma in 250 cubic centimeter amounts were given every 8 hours, the hematocrit remaining below 52 per cent on each determination. There was no evidence of sulfonamide toxicity, blood levels reached only 10 milligrams per cent at the 8th hour. Complete recovery occurred with no skin grafting being required.

CASE 4. J. S. (Chart 4.) An 8 year old negro girl was burned when her clothes caught on fire. The burning clothes were stripped from her rapidly by her mother. After soap and water cleansing, the burned areas were covered with water dispersible base ointment and modified pressure dressings (chest). Two hundred and fifty cubic centimeters of plasma was given. Hematocrit rose to 52 per cent at 8th hour but returned to 48 per cent after administration of 200 cubic centimeters of plasma, and did not rise again. The highest sulfonamide level was 21 milligrams per cent at the 18th hour. Recovery was complete after 3 skin grafting (including dermatome) operations.

B. Oil base. The representative protocols and sulfonamide absorption charts of 4 patients are shown.

CASE 5. A. C. (Chart 5.) A 30 year old colored male was burned from clothes catching fire. Apparently from history these were rapidly removed. The burned areas were



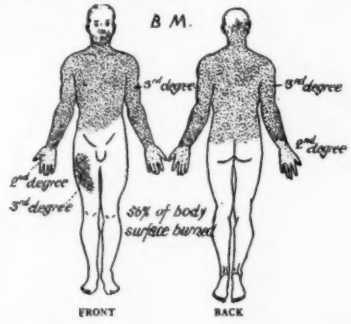


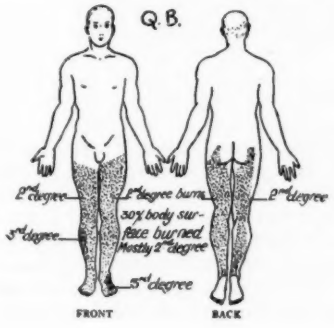
Chart 2. Extent of burn, right, and sulfanilamide level, above, in Case 2.

cleansed thoroughly of grease with soap and water and ether and oil base ointment was applied, followed by pressure dressings. Five hundred cubic centimeters of plasma was given at the 6th hour because plasma volume estimation showed only 33 cubic centimeters per kilogram, despite a normal hematocrit (44%) reading. As noted in Chart 5, blood sulfonamide concentration remained below 1 milligrams per cent ("trace"). Recovery was complete after skin grafting.

CASE 6. M. A. (Chart 6.) A 25 year old colored epileptic female was burned when her clothes caught on fire. After soap and water cleansing, the burned areas were covered with oil base ointment and occlusive dressing. Two hundred and fifty cubic centimeters of plasma was given on admission. Five hundred cubic centimeters more was given at 24th hour because hematocrit rose to 55 per cent. The blood sulfonamide level did not rise above 1.2 milligrams per cent. Recovery was complete after skin grafting.

CASE 7. E. D. (Chart 7.) An 18 year old colored female was burned from her clothes catching on fire. The burned areas were washed with soap and water, covered with oil base ointment and occlusive dressings were applied. Five hundred cubic centimeters of plasma was given on admission, repeated at 8th hour because hematocrit rose to 52 per cent. The blood sulfonamide levels never rose above 1.8 milligrams per cent. Recovery was complete after extensive skin grafting operations.

CASE 8. R. S. (Chart 8.) A 40 year old colored male was burned when his clothes caught on fire in an automobile wreck. The burned areas were cleaned with soap and water and covered with oil base ointment. Five hundred cubic centimeters of plasma was given on admission (hematocrit



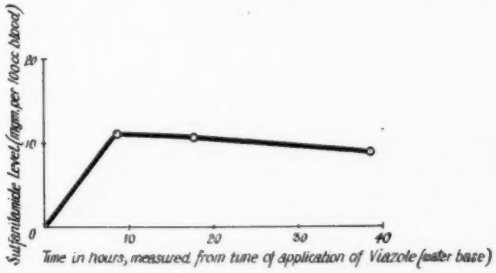


Chart 3. Extent of burn, left, and sulfanilamide level, right, in Case 3.

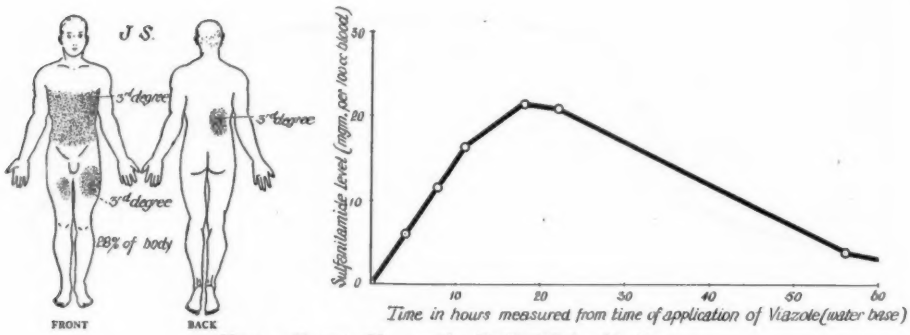


Chart 4. Extent of burn and sulfanilamide level in Case 4.

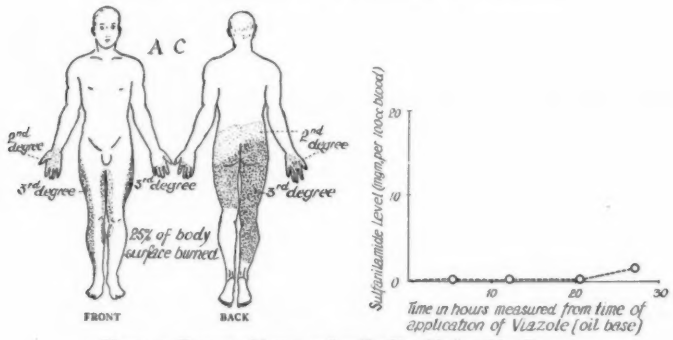


Chart 5. Extent of burn and sulfanilamide level in Case 5.

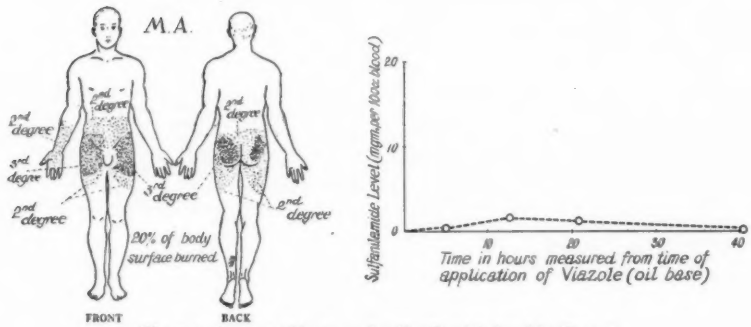


Chart 6. Extent of burn and sulfanilamide level in Case 6.

54%), and each 8 hours for 2 days because hematocrit stayed around 54 to 58 per cent, until 72 hours. The face became tremendously swollen. Blood sulfonamide levels rose to 2.8 milligrams per cent. The face and shoulders healed without grafting, but grafting was needed on upper arms.

The case studies reported here indicate without any doubt that when sulfonamides are incorporated in an oily base, very limited absorption of the drug takes place. In contrast, when the water dispersible base is used, absorption is prompt and high blood levels of the drug may be reached. In a now extensive series of burns treated with an oily base ointment (Table I) in this hospital and reported earlier (2), we have been impressed with the limited absorption of sulfanilamide from the burned surface when our own oil base ointment is

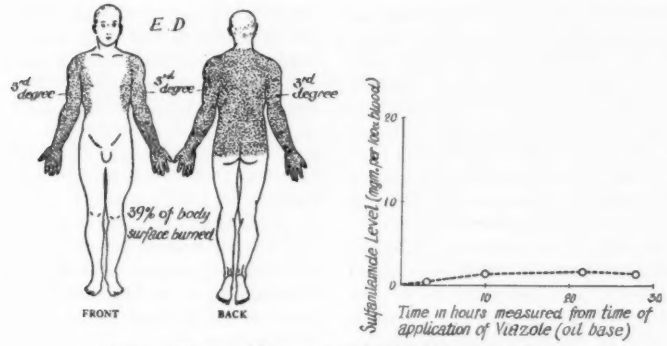


Chart 7. Extent of burn and sulfanilamide level in Case 7.

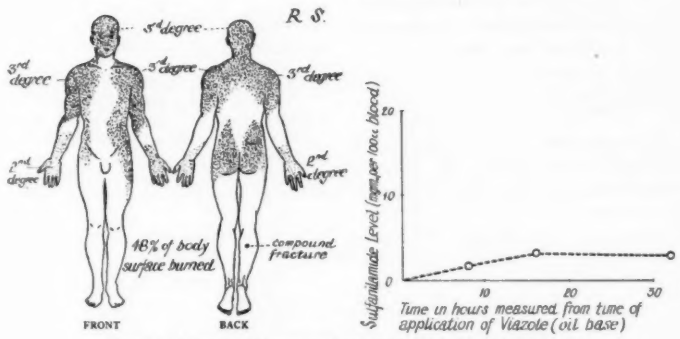


Chart 8. Extent of burn and sulfanilamide level in Case 8.

used. We have yet to see any evidence of sulfanilamide toxicity when the oil base ointment has been employed in widespread burns (up to 75% body surface).

Observations reported recently by Gurd, Ackman, Gerrie and Pritchard, and Allen, Owens, Evans and Dragstedt offer excellent supporting evidence that properly prepared sulfonamide ointments may be used with safety, and indeed with the assurance that a low incidence of infection of surgical significance will result, even if applied to large surface burns. Reference to these published works indicates that the Montreal group uses an ointment very similar to the oil base used in these studies, while the Chicago group employs an ointment very similar to our own (MCV) ointment. With each of these oil base ointments, absorption of sulfonamides has been extremely limited.

We have been impressed by the cogent article of Lockwood, who has defined with care the objectives to be desired in studies attempting to evaluate the benefits or dangers resulting from the local use of sulfonamides in wounds and burns. We are aware that studies such as have been reported by the Montreal group (3), The University of Chicago group (1), and ourselves (even though the combined series now total something over four hundred burn cases, and in which similarly prepared ointment and treatment philosophy have been used), do not settle with finality the arguments that have arisen of the wisdom of incorporating sulfonamides in burn ointments. Certainly, in these series, the incidence of infection has been gratifyingly low.

We are aware of the report of Meleney that locally applied sulfonamides did not seem to reduce the incidence of serious infection in 347 cases of burns treated by a group of investigators in different localities. In that study sulfadiazine ointment, sulfadiazine spray (Pickerell), and sulfonamide powders were applied directly to the burned area. Presumably no oil base ointments, such as described in this report, were studied.

We have continued to wash routinely and gently the burned surface with copious quantities of simple white soap and water, and to excise care-

fully the easily removed skin before applying oil base sulfonamide ointments and pressure dressings. We are in firm agreement with Koch that such an attempt at surgical cleanliness is "simply common sense." What part this practice has played in materially reducing wound and burn infection in our hands is difficult to appraise. That it is significant is borne out by our recent experience in a small number of burns in which no sulfonamide was applied to the burned surface, but the other aspects of our routine were adhered to. The incidence of burn infection was again very low. We shall continue this practice until it can be shown to our satisfaction that it is a useless step in burn therapy in the hospital. (Of course, this step is not advocated in military surgery where conditions do not allow its proper application.) The significance of infrequent dressing of the burned areas is no wise less important, no matter what ointment is used.

SUMMARY

These studies indicate that the absorption of sulfonamides from the burn surface is limited when oil base ointments are employed. In contrast, when a water dispersible base is used toxic blood levels of the drug may occur. Results of studies on burned patients indicate that oil base sulfonamide ointments can be used with safety; their use has been attended with gratifying results of low incidence of infection.

If sulfonamides are to be incorporated in an ointment for use on burns, these studies indicate that an oil base should be used. Further, studies on burn patients should be made to insure only limited, slow absorption of the drug before any such ointment is advocated for human use. In our experience an oil base composed largely of mixtures of lanolin and petrolatum has proved very satisfactory.

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CLOSURE OF DEFECTS OF THE SKULL WITH TANTALUM

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THE purpose of this paper is to stress the desirability of closing defects of the skull, to point out the advantages of tantalum implants for this purpose, to illustrate the varying conditions under which they may be used, to argue for screw fixation as compared with other means of fastening the implant, and to plead for the immediate repair of traumatic defects of the skull occurring on the field of battle.

NEED FOR CLOSING DEFECTS

The importance of closing defects in the skull, whether they result from trauma or cranial operation, has not been sufficiently stressed. This is doubtless because the cranial defect is considered unavoidable and actually beneficial in providing decompression to relieve the accompanying intracranial pressure. The obvious benefits in such cases have often blinded the surgeon to the deleterious effects of cranial defects in general. In the trephined patient the relation between the cranial defect and symptoms of dizziness, faintness, head pains, poor memory, irritability, or convulsions is frequently ignored, and the symptoms are attributed to brain damage incident to the trauma or operation. This, despite the fact that a fundamental physiologic principle is crying out for recognition, namely, that within the trephined skull the brain pulsates with each change in arterial or venous pressure, whereas in the intact skull the brain does not pulsate (3, 6). Therefore, when the surgeon leaves a defect in the skull of any significant size, he converts a nonpulsating organ into a pulsating one. The effects on the portion of the brain beneath the defect are bound to be significant, and the method of progression of the blood flow to the entire organ is necessarily altered.

There is one dictum in surgery that is seldom denied, namely, that immobilization aids wound healing. Since immobilization is important in wounds of baser tissues, it should be doubly important in the case of wounds of the brain. But when the surgeon closes the scalp over a brain wound without repairing the cranial defect, he not only has not immobilized the structures, *he has allowed them to remain in a constant state of pathologic mobility*. Furthermore, this state of pathologic mobility does not cease to exist when the brain and the scalp wound have healed but persists throughout life or until the bone defect is repaired or the scar has become so dense and inelastic that it no longer pulsates.

A common sequela to brain injury is post-traumatic epilepsy. It may occur after a cerebral contusion in the intact skull but is far more common after a penetrating brain wound. All are agreed that it is due to the cerebral scar. But Grant and Norcross found that 18 of 27 patients were improved or relieved of their seizures after an operation in which nothing was done except a repair of the cranial defect. After analyzing the results of cranioplasty in 83 patients, these authors concluded that epilepsy is benefited and the "syndrome of the trephined" is relieved in the large majority of cases by closure of the skull defect. Then may it not be assumed that some of these patients would never develop these symptoms if the skull defect were repaired immediately after the injury?

In the course of certain experiments on the rabbit brain, Falconer and Russell performed a standard decompressive operation in about 270 animals. As a corollary of these experiments they noticed certain pathologic changes in the subcortical white matter beneath the center of the site of operation in about 50 per cent of the animals with the formation of a cavity or cyst in about 30 per cent. These changes appeared to be intimately associated with cerebral herniation, and the authors concluded that they had some bearing on the pathogenesis of traumatic cerebral cysts in man. Holbourn explained these lesions by a purely physical consideration of the stresses and strains occasioned by the herniation of cerebral tissue. In my opinion, however, these authors do not attach sufficient significance to the *movement* of the brain occasioned by the constantly changing intracranial pressure.

The encephalographic finding of "migration" of the cerebral ventricle toward the site of a traumatic skull defect is familiar to every neurologic surgeon. The foregoing observations of Falconer and Russell suggest that this "migration" is not due entirely to loss of brain tissue and scar contraction from trauma *per se* but that it is partly due to a progressive gliosis and atrophy of the pulsating portion of the brain beneath the skull defect.

From the Cleveland Clinic.

MATERIALS USED FOR CLOSURE

In addition to the failure to appreciate fully the deleterious effects of cranial defects, the neurologic surgeon has been handicapped by the lack of a really suitable material for closure of them. The most widely employed material has been bone or cartilage, usually obtained from the patient. This method is traumatizing to the patient as well as time-consuming, provided sufficient care is exercised to obtain a good cosmetic result. Recently, vitallium has been employed with excellent results. Its only disadvantage is that the implant must be preformed since the material is not malleable. With the advent of tantalum it appears that an almost ideal material for closure of cranial defects has been found.

Tantalum is a pure metal with the atomic number 73 in Group V of the periodic table. It has chemical and physical properties which render it very satisfactory for covering cranial defects. First and most important, it is biologically inert, a property essential in any material used for bone repair. Second, a sheet of tantalum 0.0125 inch (0.3 mm.) thick is firm enough to afford adequate protection over a cranial defect of any size. At the same time, it is sufficiently malleable to be cut and shaped at the operating table with ordinary tin shears and a hammer. These physical properties permit tantalum to be used for closure of defects of the skull, either traumatic or surgical, without previous shaping of the implant.

LITERATURE

Carney made a survey of metals to find one as inert as vitallium, but which could be drawn into wire and worked in the cold state. He selected tantalum because it possessed these latter qualities, and his experiments showed that it was well tolerated by the tissues of the host. In 1940, Burke reported 34 clinical cases in which tantalum wire was found to be an incomparable skin suture. Venable and Stuck (16) stated that passivity, or freedom from electroactivity in the body fluids, is an essential quality of any metal for use in the body. Tantalum and vitallium had this quality, and stainless steel was "relatively" inert. Venable (15) stressed the fact that a combination of two metals should never be used even though each is inert in itself. For instance, a plate of one metal fastened in the host with screws of another metal acts as a destructive battery. Pudenz (10) in 1942 demonstrated the tolerance of brain tissue for tantalum and advocated substitution of tantalum clips for silver clips for hemostasis in neurologic surgery. Pudenz and Odom (12), in searching for a material to prevent meningocerebral adhesions, found that tantalum foil was better tolerated than was any other material tested. In an experimental study of the repair of cranial defects with tantalum, Pudenz (11) concluded that tantalum was a satisfactory alloplastic material for repair of cranial defects, since it was noncorrosive, inert in tissue, nonabsorbable, malleable, and lacked toxic ingredients. In 1943, Fulcher reported the first use of a tantalum plate in man for the repair of a cranial defect and suggested that tantalum be used for immediate repair of compound fractures of the skull. He pointed out that, although both tantalum and vitallium were inert materials, tantalum was far better for cranioplasty because it could be shaped and cut at the operating table, whereas vitallium could not. Spurling described a technique for repair of severed peripheral nerves using sutures of tantalum wire and a cuff of tantalum foil around the suture line. He presented gross and histologic evidence to demonstrate that tantalum was inert in human tissues and that scarring and fixation of repaired nerves could be reduced to a minimum by judicious use of tantalum foil.

NOTE. As this article was in preparation, Robertson reported his experiences with tantalum cranioplasty in 26 clinical cases. Fourteen of these cases were simple or compound depressed fractures of the skull, and in 5 of the latter the brain was exposed to the atmosphere for periods longer than 30 hours. Yet, to quote Robertson, "these patients were operated upon and tantalum cranioplasty was done following débridement and sulfonamide therapy without later difficulty." In the same journal DeLarue, Linell, and McKenzie (4) reported on an experimental study on the use of tantalum in the subdural space. They found serious reactive thickening of the dura mater over the tantalum in all 12 dogs, and in many there was a similar but slighter reactive thickening of the underlying arachnoid membrane. These findings are at variance with those of Pudenz and Odom (12).

HEALING OF INFECTED EXPERIMENTAL WOUNDS CONTAINING TANTALUM

In order to observe the healing of infected wounds containing pieces of tantalum, Dr. Frank C. Boyer and I performed the following experiment. Eight rabbits were selected, anesthetized with intravenous nembutal, and the backs shaved. A subcutaneous pocket was made through a skin incision 0.5 inch in length on each side of the back. One-half cubic centimeter of a fresh broth culture of Staphylococcus aureus was introduced into each wound. A piece of tantalum sheet, 0.5 inch square and 0.0125 inch (0.3 mm.) thick, was then introduced into the subcutaneous pocket on the right side, and both wounds were closed with two silk skin stitches.

Six rabbits survived the experiment. The 6 control wounds in these animals all became in-

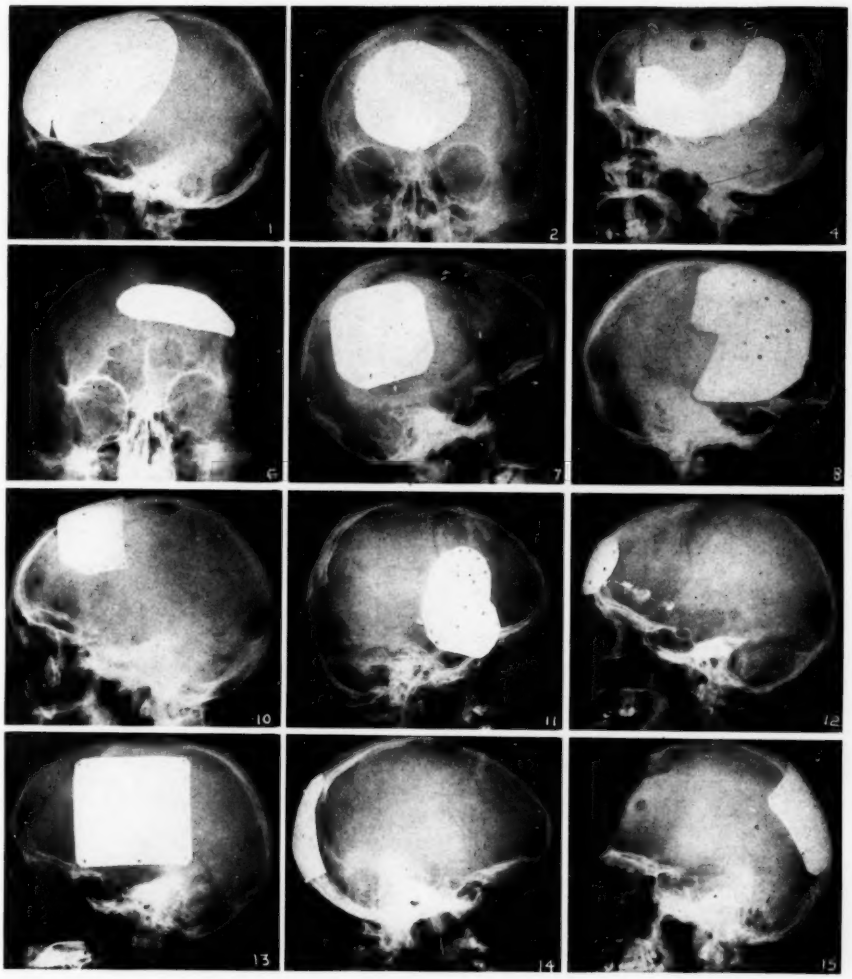

Fig. 1. Postoperative roentgenograms. Numerals are case numbers.

fected. Five of the tantalum wounds became infected, the sixth one remaining healthy. Infection appeared first in the control wounds in 4 instances, first in the tantalum wound in 1 case, and simultaneously in both wounds in 1 case. Infection in each case appeared between the 5th and the 10th day. The wounds were incised and drained between the 10th and the 15th day, and all healed between the 19th and the 31st day. In 1 case the tantalum was discharged from the wound. In this rabbit necrosis and sloughing of the skin occurred with the formation of large ulcers at the site of both wounds. There was no appreciable difference in the rate of healing of the wounds containing tantalum and the controls.

CASE REPORTS

At the Cleveland Clinic tantalum has been used to repair cranial defects in 15 cases (Fig. 1). In 4 cases (1, 2, 3, 13) tantalum was used to cover defects caused by removal of bone invaded by tumor tissue. In 3 cases (4, 8, 10) tantalum was used to repair a defect caused by removal of bone with the rongeur when the original craniot-

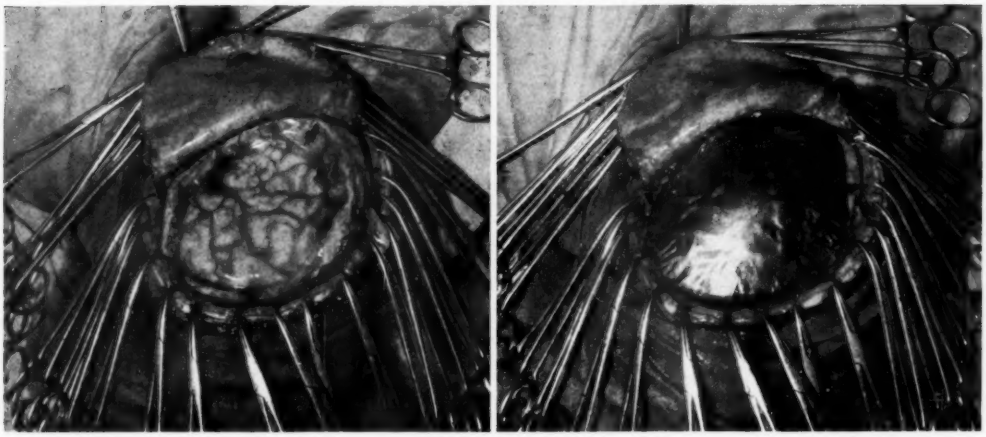

Fig. 2. Case 1. a, The cranial defect 6 weeks after tantalum cranioplasty. The brain is covered by a thin translucent membrane which formed beneath the original implant. b, The second implant in place.

omy opening was not advantageously placed for removal of a brain tumor. In 2 instances (7, 11) operations were performed for recurrent brain tumor. The bone immediately over the tumor was removed with the rongeur without attempting to lift the previous bone flap. This shortened the procedure and provided a small but more effective exposure. After removal of the growth the defect was covered with a tantalum implant. In 3 instances (5, 9, 14) tantalum was used to repair an old cranial defect. In 2 cases (6, 12) the implant was used for the immediate repair of a compound fracture of the skull. In the remaining case (15) tantalum was used to close the bony defect immediately after the excision of multiple brain abscesses, and primary union resulted.

The results in these clinical cases substantiate the findings of earlier investigators regarding the advantages of tantalum for cranioplasty.

Case 1. Repair of cranial defect caused by excision of metastatic tumor of the frontal bone. Inadequate fixation necessitated second operation. A woman, aged 59 years, had a single metastatic lesion in the left frontal bone from a malignant adenoma of the thyroid, which had been removed 1 year before. The lesion measured 2.5 inches in diameter on x-ray films. Operation was performed on March 2, 1943. A flap of scalp was reflected, leaving the periosteum attached to the bone. Block removal of the bony tumor was then accomplished with wire saws. Some tumor tissue remained adherent to the outer surface of the dura, which was therefore widely excised.

A roughly circular piece of tantalum 0.020 inch (0.508 mm.) thick was cut and fashioned with a hammer on a concave wooden block to conform to the shape of the skull. The edges of the implant extended about 0.5 inch beyond the bony margins of the opening. Shallow grooves were cut in the outer table of the skull to give the edges of the implant some degree of fixation. The scalp was closed over it.

During the postoperative course, the scalp over the implant became distended with fluid, and when the patient leaned forward, the implant slipped forward a short distance. Because the movement of the implant and the accompanying clicking sound annoyed the patient, a second operation was performed on April 12. The implant was found to be enclosed in a thin-walled sac, with an inner surface of young translucent dura. A new implant was fashioned from a sheet of tantalum 0.0125 inch (0.3 mm.) thick and was fastened to the skull with two tantalum wire sutures (Fig. 2).

Fluid again collected beneath the scalp for some weeks. It did not require aspiration and eventually subsided. There was no movement of this implant. The thinner material used at the second operation was shaped more accurately and with less effort than that used for the first implant.

When the patient was last seen 14 months later, the cosmetic result was excellent. However, additional cranial metastases had appeared.

Case 2. Repair of cranial defect caused by excision of hemangioma of frontal bone and sinuses. Introduction of tantalum implant into frontal sinuses did not interfere with healing. A woman, aged 55 years, had a hemangioma of the skull 2 inches in diameter, which produced an unsightly swelling in the middle of the forehead. Roentgenograms showed extension into the upper half of both frontal sinuses.

Operation was performed on March 8, 1943. A horseshoe-shaped scalp flap was reflected down to the eyebrows leaving the periosteum attached to the bony swelling. The entire thickness of the involved bone including the upper half of the frontal sinuses was removed with a rongeur. The dura was left intact. A roughly circular sheet of tantalum 0.015 inch (0.375 mm.) thick was fashioned to cover the defect. The implant rested on the outer table of the skull to which it was fixed by two tantalum wire sutures, with the anterior edge lying on the bony septum separating frontal sinuses just behind their anterior walls. The scalp was closed with a single buried tier of interrupted black cotton.

To prevent infection from the nasal passages during convalescence, the patient was given sulfathiazole and was cautioned not to blow her nose. Recovery was uneventful.

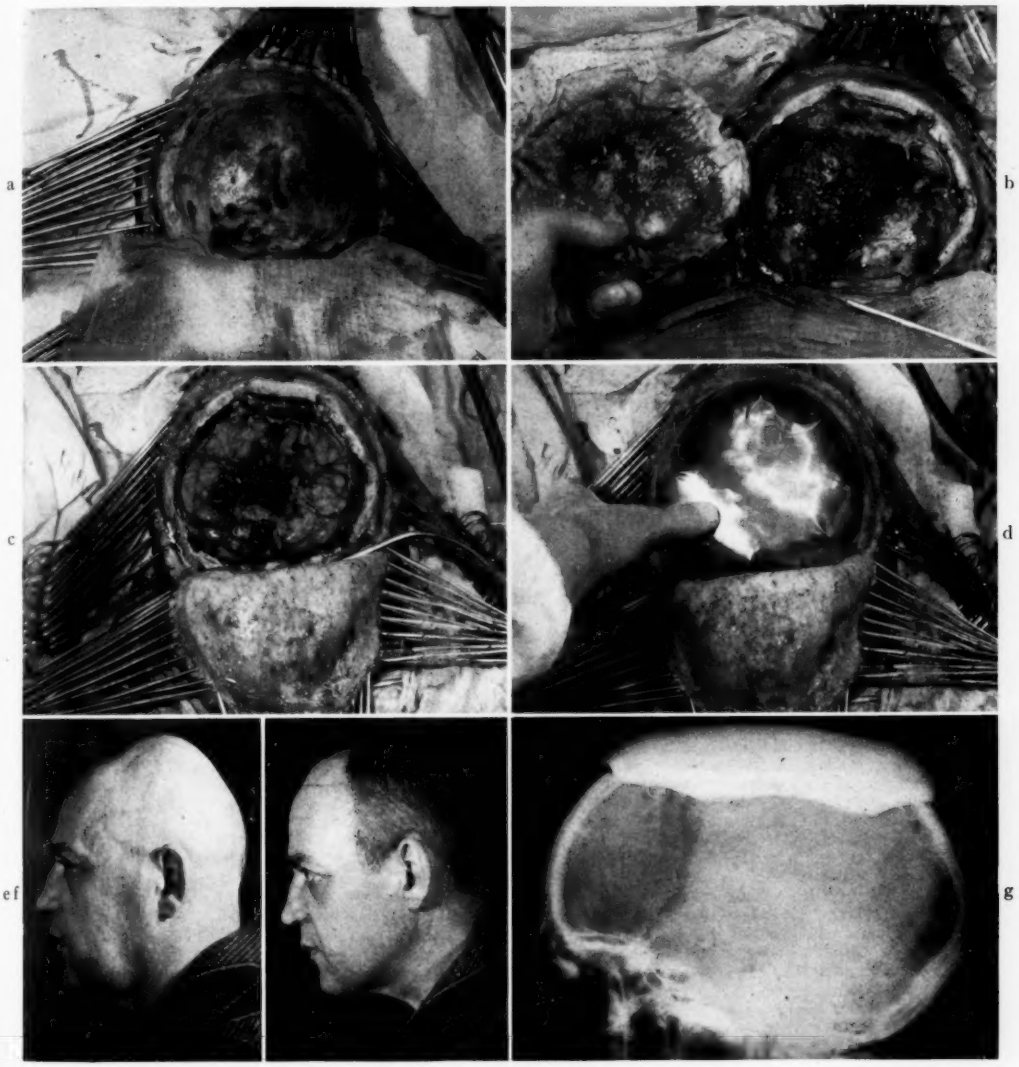

Fig. 3. Case 3. a, The scalp has been reflected showing the tumor of the skull covered with periosteum. b, The inner surface of the bone is invaded by the tumor. c, The meningioma together with the involved dura, sagittal sinus, and falx has been incised. d, The tantalum implant in place. e, Lateral view of patient before operation. f, Lateral view of patient after operation. g, Postoperative roentgenogram.

and no fluid accumulated over the implant.

Three months after operation when a head clamp was tightened in the course of x-ray examination of the skull, the patient felt something snap. For 2 months thereafter she occasionally heard clicking sounds in her head. Apparently the tantalum wire sutures gave way under the stress, and the implant occasionally moved.

When the patient was seen 14 months after operation, the cosmetic effect was excellent.

CASE 3. Repair of large cranial defect caused by excision of bone invaded by parasagittal meningioma. A man, aged 45 years, had a parasagittal meningioma at the vertex with extensive involvement of overlying bone. On March 9, 1943, the involved calvarium was removed with a wire saw

Fig. 4a.

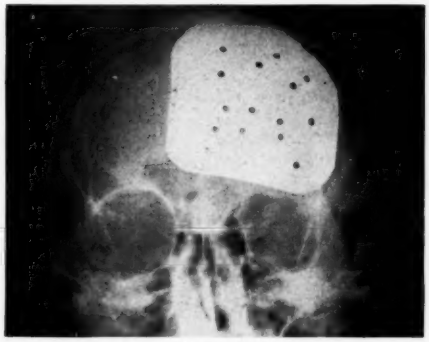

Fig. 4b.

Fig. 4. Case 5. a, Before tantalum cranioplasty. b, Six weeks after operation. c, Postoperative roentgenogram.

leaving a defect 5.5 inches in diameter. The meningioma with the involved dura, sagittal sinus, and falx was excised. A circular sheet of tantalum, 0.0125 inch (0.3 mm.) thick and 6 inches in diameter, was fashioned to cover the large bony defect and was fastened to the bone with four tantalum wire sutures (Fig. 3). The scalp was closed with a single buried tier of interrupted black silk sutures.

A large amount of cerebrospinal fluid accumulated beneath the scalp flap and was aspirated daily for 2 weeks. The amount of fluid rapidly decreased until aspiration was no longer necessary.

When the patient was last seen 12 months after operation, the cosmetic result was excellent.

Case 4. Repair of cranial defect caused by removal of additional bone with rongeur during craniotomy for glioma. Autopsy findings 8½ months later. A man, aged 38 years, was operated upon May 5, 1943. A well circumscribed glioma was removed from the right temporoparietal region. The dura was closed. After the section of bone was replaced, a piece of tantalum 0.0125 inch (0.3 mm.) thick was fashioned to cover a large semilunar defect in the temporal region where additional bone had been removed with the rongeur. For fixation little tongues were cut into the edge of the implant, turned down at right angles, and inserted into small holes bored in the outer table of the skull. The bone flap was secured with tantalum wire sutures. The scalp was closed with a single buried tier of interrupted black cotton sutures. No fluid accumulated in this case. The cosmetic effect was excellent.

The patient returned to work 2 months after operation. Five months later signs of recurrence of the tumor appeared, and he died on January 22, 1944, 8½ months after operation. At autopsy the tantalum implant was found to be enclosed in a smooth walled, tightly fitting sac which contained no fluid. The outer wall of the sac was about 0.5 millimeter thick and was attached to the under surface of the temporal muscle. The inner wall of the sac consisted of a thinner translucent membrane investing the margins of the bony defect and the outer surface of the exposed portion of the dura. This membrane showed no microscopic evidence of irritation. Where the cortex had been incised for removal of the growth, it adhered in one small area to the dura. The tantalum implant was as smooth and bright as when it was inserted.

Case 5. Repair of old cranial defect caused by previous excision of left frontal bone for osteomyelitis. A man, aged 20 years, had an operation for osteomyelitis 20 months previously. The left frontal bone was removed including the frontal sinus, supraorbital ridge, and anterior portion of the roof of the orbit. The bone did not regenerate, and the patient wished to have the unsightly defect repaired. He was subject to frequent grand mal seizures.

On June 11, 1943, the scalp incision was reopened, and the scalp reflected from the dura. The periosteum was freed from the margins of the bony opening except where the supraorbital ridge was missing in front. During dissection the dura was punctured in two places, and the mucous membrane of the left frontal sinus was inadvertently opened. A piece of tantalum 0.0125 inch (0.3 mm.) thick was fashioned to cover the defect and perforated with a hand punch. The implant fitted snugly without fastening. The scalp was closed over it. During convalescence the patient was given sulfadiazine to combat possible infection from the nasal passages and was cautioned not to blow his nose. Recovery was uneventful, and there was no fluid accumulation. Although the supraorbital ridges were still not symmetrical, the cosmetic result was satisfactory (Fig. 4). When last heard from, 13 months after operation, he had suffered no more convulsive seizures.

Case 6. Immediate repair of cranial defect from compound comminuted fracture of the skull with laceration of the brain. While endeavoring to remove a heavy tire, a young man, aged 24 years, was struck in the midfrontal region by the rim of a truck wheel. He sustained a compound comminuted fracture of the skull with laceration of the brain and dura. He was not rendered unconscious immediately but lost consciousness within an hour and had a series of five generalized convulsions.

On June 11, 1943, 14 hours after injury, he was operated upon under pentothal anesthesia. The margins of the linear scalp wound were trimmed and retracted, and fragments of loose bone were removed, leaving a bony defect measuring 1 by 2.5 inches. Macerated brain tissue was removed by gentle irrigation and suction, and a bleeding point on the cortex was controlled by electrocoagulation. The lacerated dura and sagittal sinus were not bleeding and were not disturbed. A piece of tantalum 0.0125 inch (0.3 mm.) thick was fashioned to cover the bony defect and was

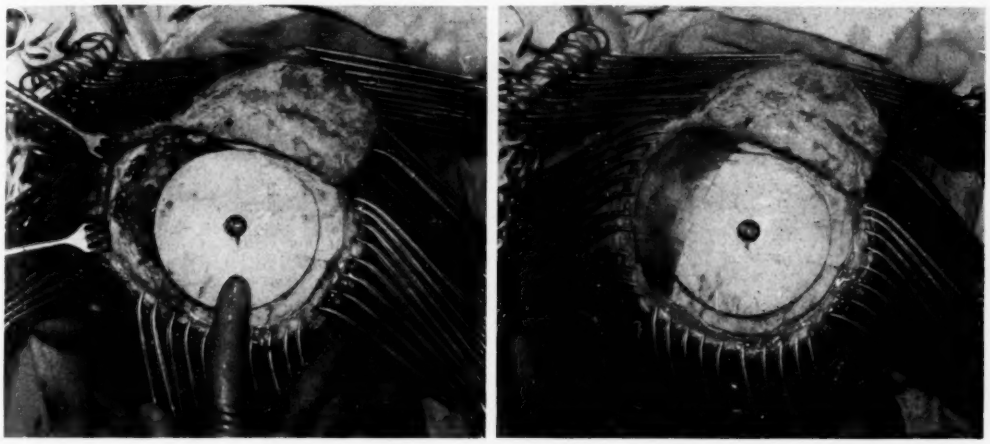

Fig. 5. Case 10. a, left, Cranial defect remaining after replacement of section of bone removed by craniotome. b, The tantalum implant fastened by means of two tantalum screws.

simply laid on the outer table of the skull. Powdered sulfanilamide was introduced, and the wound was closed with a single buried tier of interrupted black cotton sutures in the galea. No drainage was used. Oral administration of sulfadiazine was begun the next day.

The wound healed quickly without fluid accumulation, and the patient was discharged free from symptoms on the 12th postoperative day. He resumed work as a truck driver within 2 months. He was last seen 9 months later. He had lost no time from work, and the cosmetic result was good.

CASE 7. Repair of cranial defect caused by operation for recurrent glioma. Reoperation 11 months later. A woman, aged 21 years, had a left parietal glioma removed 6 years previously. She had symptoms of recurrence, and x-ray disclosed a large calcified tumor of the left parietal lobe.

Operation was performed on August 16, 1943. Instead of elevating the large bone flap of the previous operation, the skull overlying the growth was removed with a rongeur. The tumor was then excised. The lateral ventricle was widely opened during dissection of the growth. The dural defect was not repaired. The cranial defect was covered with a perforated sheet of tantalum 0.0125 inch (0.3 mm.) thick held in place with two tantalum wire sutures.

Fluid accumulated between the scalp and the implant for 23 days and was removed by daily aspiration or lumbar puncture. The fluid no longer accumulated when the patient was able to be out of bed. She was discharged 28 days after operation.

Ten months after operation symptoms developed suggestive of a recurrence of the growth. Another operation was performed on July 22, 1944. The scalp over the implant was fluctuant. An aspirating needle encountered clear, very faintly xanthochromic fluid between the scalp and the implant. This fluid contained no cells, and the total protein content was 245 milligrams per 100 cubic centimeters. A flap of scalp was reflected to uncover the implant, and this maneuver was accompanied by a gush of fluid. The under surface of the scalp was not adherent to the implant but was covered with a smooth, thin membrane. The implant was clean and shining and only loosely anchored by tantalum sutures. The sutures were divided, and the implant was removed. There was no membrane beneath the implant but a huge cavity, which proved to be an enormously dilated left ventricle. The foramen of Monro was not patent. The recurrence of symptoms was thought to be due to obstruction of the ventricle rather than to recurrence of the tumor. The choroid plexus in the obstructed ventricle was treated with electrocautery, after which the implant was replaced and fastened with tantalum screws and the scalp was closed. When the patient was discharged on the 10th day after operation, the symptoms were subsiding. There was a very slight amount of fluid over the implant.

CASE 8. Repair of cranial defect occasioned by removal of incorrectly localized meningioma; fixation inadequate. A woman, aged 43 years, presented symptoms of tumor of the left temporal lobe. Operation was performed on August 27, 1943. A circular section of bone over the temporal lobe was removed with a craniotome. The tumor was located much farther forward than was anticipated, and most of the left frontal bone had to be removed with a rongeur in order to expose it. After a long, difficult operation accompanied by severe blood loss and surgical shock, a very large meningioma (245 gm., 13 by 7 by 7 cm.) was excised which had originated on the anterior portion of the falx. The section of bone was replaced and fastened with a tantalum suture, but an enormous defect in the frontal bone remained. A piece of tantalum 0.0125 inch (0.3 mm.) thick was laid across the defect and the scalp was closed over it. The dura was only partially closed. No attempt was made to fix the implant. It was not anticipated that the implant would stay in proper position, but it was hoped that it would render subsequent repair easier. The patient had a very stormy convalescence complicated by serious decubitus ulcers, which prolonged the hospital stay to 8 weeks. Large quantities of fluid were aspirated from beneath the scalp every day or two for the first 6 weeks. On one occasion culture of this fluid revealed Staphylococcus albus. It was believed that this patient had Staphylococcus albus meningitis, which responded to the administration of sulfadiazine.

When the patient was last seen, 3½ months after operation, the implant was well fixed but was located about 3 centimeters posterior to its original position, leaving a defect in the left frontal region just below the hairline. The patient wishes to return for repair of this defect, which will

Fig. 6. Author's equipment for cutting, shaping, and perforating the implant: tin shears, metal punch, tantalum plate (6 by 6 inches), round headed hammer, concave wooden block.

probably be closed with another strip of tantalum, leaving the original implant in its present position.

CASE 9. Repair of old cranial defect caused by removal of meningioma. Screw fixation of implant. Death from meningitis secondary to pre-existing dermatitis. A man, aged 54 years, had a very large left parietal defect caused by removal of a parasagittal meningioma 4 months previously. At that time it had been impossible to replace the bone flap because of brain swelling. When the patient's scalp was shaved in preparation for cranioplasty, he was found to have a dermatitis. The infection was treated for 6 days, and operation was performed on October 18, 1943. The scalp flap was reflected, the margins of the bony opening were exposed, and a piece of tantalum was fashioned to cover the cranial defect. Three tantalum screws were used to fasten the implant to the margins of the bony opening, and the wound was closed. Because of the previous unhealthy condition of the scalp, the patient was given sulfadiazine by mouth. On the 18th day of convalescence he had a convulsion followed by a rising temperature and a collection of fluid beneath the scalp. He died 6 days later of fulminating Staphylococcus aureus meningitis despite intensive sulfonamide therapy. Death was attributed to an error in judgment in not treating the dermatitis for a sufficiently long period before operation.

CASE 10. Repair of cranial defect caused by removal of additional bone with rongeur to expose meningioma. Screw fixation of implant. A man, aged 57 years, presented symptoms of tumor in the right sensorimotor area. On December 8, 1943, a circular section of bone was removed with a craniotome, and a meningioma was disclosed, which extended beyond the anterior edge of the bony opening. Additional bone was removed with a rongeur in order to uncover the growth entirely. The tumor was removed and the section of bone was replaced. The large dural defect was not repaired. A strip of tantalum was fashioned to cover the bony defect and perforated with a hand punch. While the assistant held the implant in position, the operator drilled two holes in the skull through the previously selected perforations in the upper and lower margins of the implant. Into these holes were placed tantalum screws, which drew the implant tightly against the outer table of the skull, providing a very firm fixation (Fig. 5). The scalp was closed with a single buried tier of interrupted black silk sutures. The patient was discharged on the 22d postoperative day. The cosmetic result was excellent when he was last seen 7 months after operation.

CASE 11. Repair of cranial defect resulting from operation for recurrent glioma. Screw fixation of the implant. A lad, aged 13 years, had a recurrent cystic astrocytoma of the right temporal lobe. At operation on January 26, 1944, instead of re-elevating the previous bone flap which was not advantageously placed, a large opening was made with the rongeur in the right temporal region through a linear incision. After removal of the tumor, the dura was loosely closed, and the bony defect was covered with a perforated tantalum implant. The implant was fastened to the skull by means of two tantalum screws. The wound was closed with two buried tiers of black silk sutures. During convalescence fluid was prevented from collecting beneath the scalp by means of light pressure with an elastic bandage. The patient was discharged on the 10th postoperative day. When last seen 3 months later, the cosmetic result was excellent.

CASE 12. Immediate repair of cranial defect in a gunshot wound of the brain. Screw fixation of implant. A woman, aged 34 years, was struck in the right frontal region with a 38 caliber bullet. She was not unconscious, and there was no paralysis or convulsion. X-ray showed a defect in the frontal bone above and to the right of the frontal sinuses. Particles of lead and bone outlined a tract leading deep into the right frontal lobe.

Operation was performed on February 8, 1944, 7 hours after injury. The patient was anesthetized with sodium pentothal. Removal of the emergency dressing disclosed a mass of extruded macerated brain tissue concealing the wound. The scalp was shaved and cleansed revealing a wound of entrance and a wound of exit separated by a bridge of skin 0.5 inch wide. The bullet had apparently glanced. The bridge of skin was divided, the edges trimmed, and the wound lengthened by an incision at both ends. The wound was irrigated with saline, and a quantity of macerated brain tissue, clot, and bone fragments was removed from the bullet tract with an aspirator. The bony defect was enlarged with a rongeur so that bleeding points in the brain and dura could be adequately controlled with electrocautery. The defect measured 1 by 2 inches. A small quantity of sulfanilamide crystals was dusted on the lacerated brain. A piece of tantalum 0.0125 inch (0.3 mm.) thick was shaped, perforated, and placed over the cranial defect. A single tantalum screw was used to fasten the implant to the outer table of the skull. The scalp was closed with a buried tier of interrupted black silk sutures in the galea and two superficial sutures in the skin. The patient was given a plasma transfusion during the operation. Oral administration of sulfadiazine was begun the next day.

The wound healed rapidly without evidence of inflammation. Convalescence was uneventful, and the patient left the hospital on the 14th postoperative day. The cosmetic result was excellent. She showed no emotional reaction to the tragedy in which she lost her family and almost lost her life. This symptom was attributed to the damage to the right frontal lobe. She resumed her job at a war plant 7 weeks after the accident and has remained well to date.

CASE 13. Repair of cranial defect caused by removal of epidermoid of skull. Screw fixation of implant. A man, aged 25 years, had an epidermoid of the anterior portion of the left parietal bone for 15 years. The defect on the x-ray film measured 4 centimeters in diameter. Removal was indicated because of a prominent external swelling.

On February 18, 1944, a flap of scalp was reflected including the upper portion of the temporal muscle. The lesion was removed in one piece with a Hudson drill and wire saws. The dura was not incised. A sheet of tantalum 0.0125 inch (0.3 mm.) thick and 9 centimeters square was fashioned to conform to the shape of the skull. The implant was perforated, placed over the cranial defect, and

fastened to the skull with three tantalum screws. The scalp was closed with a single buried tier of interrupted black silk sutures. Because of the relaxed condition of the scalp covering the implant, a postoperative hematoma developed between the scalp and the implant. By the 12th postoperative day, this clot had largely liquefied, and it was removed by aspiration. When the patient was last seen 3 months after operation, the cosmetic result was excellent.

CASE 14. Repair of old cranial defect caused by injury. Screw fixation of implant. A lad, aged 13 years, had a cranial defect over a porencephalic cyst in the right occipital region. The cranial defect was said to have appeared after a severe injury to the back of the head at the age of 7 months. The patient was subject to frequent jacksonian convulsions.

On March 22, 1944, the scalp was reflected, and the cranial defect was enlarged with a rongeur. The exposed portion of the dura with the attached cerebral scar was excised. A piece of tantalum 0.0125 inch (0.3 mm.) thick was fashioned to cover the defect, perforated, and fastened to the outer table of the skull with three tantalum screws. The scalp was closed with a buried tier of interrupted black silk sutures. Fluid collected between the scalp and the implant. From 70 to 100 cubic centimeters of fluid was removed daily either by aspiration of the wound or by spinal puncture. After the 5th postoperative day this accumulation was controlled by light pressure with an elastic bandage. The patient was discharged on the 10th day. When last seen 15 weeks after operation, the cosmetic result was good, and there had been no further convulsions.

CASE 15. Repair of cranial defect after excision of multiple brain abscesses. Primary healing of infected wound. A young man, aged 17 years, was hospitalized for 3 months after a frontal craniotomy for osteomyelitis of the skull complicating frontal sinusitis. During this time he had repeated operations for the drainage of brain abscesses of the left frontal and right occipital lobes. The organism was a penicillin sensitive anaerobic streptococcus. On June 27, 1944, the patient was extremely ill with meningitis and multiple brain abscesses in the right parieto-occipital region. On this date a flap of scalp was reflected, and a bony opening 2.5 inches in diameter was made over the site of the abscesses. The dura was excised, and the diseased brain was cut away with the electrosurgical loop to a depth of more than 2 inches. Several small subcortical abscesses were opened and removed. Palpation then disclosed a large firm subdural abscess plastered against the right side of the falx. This was incised and about 2 ounces of thick pus escaped. The outer wall of this abscess was excised, the medial wall was left attached to the falx. Ten cubic centimeters of penicillin solution, 1000 units per cubic centimeter, was introduced into the cavity in the brain tissue, after which a perforated tantalum implant was placed over the bony opening and fastened to the outer table of the skull with two tantalum screws. The scalp was then tightly closed with a buried tier of interrupted black silk stitches in the galea. Drainage was not instituted, and the wound was not aspirated. For the next 48 hours the patient received 10,000 units of penicillin every 4 hours intramuscularly, 10,000 units every 4 hours was injected beneath the scalp over the tantalum plate, and 10,000 units was given intrathecally every 12 hours. After 48 hours the intrathecal injections were discontinued, and the injections beneath the scalp were reduced to twice a day. The intramuscular injections were continued until the 16th postoperative day. The temperature reached normal on the third day after operation and remained normal.

Convalescence was very smooth, and the patient was discharged 3 weeks after operation. At no time was there any evidence of inflammation in the wound. When last seen 12 weeks after operation he was free from symptoms and the cosmetic result was good.

As the result of experience with 15 cases reported, it appears that tantalum is an almost ideal material for the repair of cranial defects. It can be used to repair either surgical or traumatic skull defects, whether they are fresh or old. A sheet of tantalum 0.0125 inch (0.3 mm.) thick is sufficiently rigid to afford adequate protection over a cranial defect of any size, yet it can be readily shaped at the operating table to conform to the contour of the skull. The necessary implements are a pair of tin shears, a metal punch, a round headed hammer, and concave wooden block (Fig. 6).

Small tantalum screws provide the best method for fastening the implant to the skull. In addition to providing perfect fixation, they permit the operator to draw the edges of the implant down against the skull and thus save time which would otherwise be spent in meticulous shaping of the implant to the contour of the skull. Unfortunately, tantalum screws of the proper size are not yet on the market. Those used in the cases described were made by hand.[1]

In these 15 cases there were 7 instances of large, unrepaired dural defects beneath the implant. In 5 of these (1, 4, 7, 9, and 13) significant collections of cerebrospinal fluid developed between the scalp and the implant, which persisted for some weeks, apparently until the newly formed dura became water-tight. The fluid collection in no case prolonged the patient's hospital stay nor did it impair the final result. In later cases the accumulation of fluid was controlled by a few turns of elastic bandage over the dressing. Perforating the implant had no effect on the frequency of occurrence or the duration of fluid collection. This accumulation of fluid could probably be decreased, or perhaps prevented entirely by closing the dural defect with a dural substitute. However, in my opinion, it is better to accept this fluid accumulation and treat it by using an elastic bandage or by aspiration while the new dura forms rather than to place another extraneous material next to the brain. The accumulation of cerebrospinal fluid over the implant is not an irritative phenomenon. It occurs because the scalp is not adherent to the smooth surface of the implant, and therefore the cerebrospinal fluid pressure lifts the scalp away from it.

There was one infection in this series of 15 cases, and it resulted in the patient's death. It was due to an error in judgment in operating soon after a

[1]Since completion of this article it has been announced that tantalum screws for skull plates will be obtainable on or about April 1, 1945.

scalp infection and was not due to the presence of the tantalum implant.

One of these patients (Case 4) came to autopsy 8½ months after operation. The implant showed no evidence of corrosion. It was enclosed in a thin, smooth walled membrane showing no microscopic evidence of irritation, nor did the bone beneath the implant show evidence of irritation or proliferation. The dura beneath the implant appeared just as normal as that beneath the intact portion of the skull. The findings at this autopsy and at the second operations in Cases 1 and 7 demonstrate that, in cases of brain tumor in which subsequent operations are anticipated, the neurologic surgeon may do well to discard the bone flap and close the defect with tantalum. At the next operation he will be spared the difficult, traumatizing, and time-consuming procedure of re-elevating the adherent bone flap.

One disadvantage of tantalum for cranioplasty is its x-ray density. Because of its high atomic weight, tantalum casts a dense shadow on the x-ray film, obscuring everything beneath it. In cases of brain tumor in which postoperative x-ray therapy is contemplated, the presence of a tantalum implant may require special technique since it will act as a filter and also a secondary radiator. Only careful study of the individual conditions will enable the roentgenologist to deliver a satisfactory dose to a tumor beneath a tantalum implant.

POSSIBILITIES IN WAR SURGERY

Tantalum cranioplasty will be of great value in the next few years for the secondary repair of war wounds of the skull. The possibilities of primary repair in these cases is illustrated in Cases 6 and 12. It will be difficult to overcome the surgical prejudice against embedding a foreign material in a contaminated wound, but Case 15 shows that even the presence of frank infection is not an absolute contraindication to the use of tantalum. Because of its simplicity, immediate tantalum cranioplasty for head wounds is entirely feasible in war surgery (17). It need not prolong the operation of débridement and closure by more than 5 minutes. In its simplest application no special tools are required. The sheet of tantalum can be cut with ordinary scissors, bent to the proper contour in the operator's hands, and simply laid over the skull defect without fastening. Because of possible undesirable electrolytic effects, the operator should endeavor to remove all metallic foreign bodies from the immediate vicinity of the implant. In contaminated wounds the implant should be perforated to allow passage for an exploring needle should a brain abscess develop in the tract of the missile.

Immediate tantalum cranioplasty in penetrating wounds of the brain will immobilize and protect the traumatized brain and scalp during the healing process and will thus reduce the incidence of cerebral fungus and post-traumatic epilepsy. It will obviate the need for secondary cranioplasty. Present indications are that it will not increase the percentage of infection in these wounds. It will spare the patient the additional hospital days and also the risk of a secondary cranioplasty.

CONCLUSIONS

1. The importance of the repair of defects of the skull has not been sufficiently stressed in the past.

2. A sheet of tantalum constitutes an almost ideal material for the repair of cranial defects.

3. It should be more widely employed for the immediate repair of compound fractures of the skull.

4. Small tantalum screws constitute the most satisfactory means of fastening the tantalum implant to the outer table of the skull.

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THE INTRAVENOUS INJECTION OF A PROTEIN DIGEST SOLUTION IN SURGICAL PATIENTS

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IN recent years, there has been a growing interest in, and an appreciation of, the need for a source of parenteral protein on the part of both the surgeon and the internist. The nutrition of the surgical patient has suffered particularly due to inadequate intake and postoperative loss.

Elman, Farr, Brunschwig, Shohl, Messinger and Landesman have reported results on the intravenous administrations of a protein digest solution prepared from enzymatic digest of purified casein. These investigators have shown that such a preparation may be given to man with beneficial results.

This communication constitutes a report on the effect of the rate of administration and the incidence of reaction when a protein digest is administered intravenously. A brief discussion of the need and value of such a preparation postoperatively is also included.

PREPARATION OF MATERIALS USED

The protein digest solution used was prepared from an enzymatic digest of a mammalian protein. The crude digest is purified according to a procedure which removes all the toxic and otherwise undesirable constituents, maintains the sterility of the mixture, and yields a stable, heat sterilized, pyrogen-free solution with a *p*H of approximately 6.5. The end-product is approximately a 6 per cent solution of protein digest which contains free amino acids and polypeptides. At least 50 per cent of the nitrogen is present as free α amino nitrogen. The solution is free of undigested proteins and proteoses, and not more than 1 per cent of the total nitrogen is present as ammonia nitrogen. It also contains adequate amounts of the essential amino acids to support growth and to maintain nitrogen equilibrium. Each lot of solution is shown to be pyrogen-free by tests on rabbits, and the absence of vasomotor substances is shown by blood pressure tests on dogs. Nitrogen balance experiments on dogs are also performed with each batch in addition to the various chemical and bacteriological control procedures. We have used a total of 8 different batches of this material, which was prepared in the laboratory on a small scale. The solution is a clear, light amber fluid.

Each lot of solution conforms approximately to the following specifications:

	Gm. in 100 c.c. of solution
Total solids	6.0
Total nitrogen	0.625
α amino nitrogen (50–60% of the total nitrogen)	0.325–0.39
Ammonia nitrogen	0.004–0.008
Ash	0.85

METHOD OF STUDY

The patients who received the protein digest intravenously were selected from the surgical service and were from among those who needed a source of parenteral protein. Generally, they represented the overall picture of the more ill, indigent patients of a city hospital (Gallinger Municipal Hospital, Washington, D.C.).

An individual record was kept of each intravenous injection in which the time, rate of flow, and the presence of any reaction were carefully recorded. All intravenous infusions were observed by one of us (J.J.W.) or a technician, throughout their administration. The equipment used for the injection was cleaned and sterilized by the accepted technique to remove pyrogens.

There were a variety of surgical diseases among the patients who received the protein digest solution. Table I represents the diseases and number of patients in each disease group. It is obvious from this chart that patients suffering from the more serious surgical conditions and whose food intake was markedly inadequate were the ones who received the protein digest solution.

Amount injected. The average amount of protein digest solution given in each injection was approximately 1 liter. The total amount administered to any one patient varied considerably; the minimum being 500 cubic centimeters, and maximum 21 liters. The latter amount was given during a period of 21 days. There were 10 patients in the series who received from 7 to 11 liters in 5 to 11 days. The total amount administered

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TABLE I.—CASES RECEIVING PROTEIN DIGEST

Disease	No. of patients
Ruptured diverticulum of the colon with peritonitis	1
Ruptured liver with peritonitis	1
Ruptured appendix with peritonitis	3
Carcinoma of the stomach with gastric resection	2
Peptic ulcer with gastric resection	2
Intestinal obstruction	5
Cholecystitis	4
Appendicitis with appendectomy	4
Tuberculous peritonitis	2
Stab wound of the abdomen	2
Gunshot wound of the abdomen	1
Acute pancreatitis	1
Pelvic abscess	1
Abdominal abscess	1
Rectal fistulas	1
Perforated peptic ulcer	1
Burns	3
Hemorrhoids	2
Multiple lacerations	1
Inguinal herniorrhaphy	1
Strangulated inguinal hernia with repair	1
Papillary cyst adeno carcinoma with hypoproteinemia	1
Cirrhosis of the liver with hypoproteinemia	1
Intestinal fistulas	1
Carcinoma of the descending colon and intestinal obstruction	1
Carcinoma of the transverse colon and intestinal obstruction	1
Lymphopathia venerum with combined abdomino-perineal resection	1
Bulbar poliomyelitis	1
Safety pin in duodenum with a duodenostomy	1
Abdominal evisceration	1
Total	49

intravenously during this study was 165.5 liters.

In view of the nitrogen content, 1 liter of the protein digest solution contains approximately 6.25 grams of nitrogen or is equivalent to approximately 60 grams of protein. Thus the administration of 1 to 3 liters a day would give a patient the equivalent of 60 to 180 grams of protein. One patient in this study who received 21 liters in 21 days, received the equivalent of approximately, 1,260 grams of protein. This is a large secondary supply to give an acutely ill patient whose intake is markedly limited. The use of such protein digest intravenously has an important sparing action upon the body proteins which are drawn upon when the need is great and the intake is inadequate.

Rate of administration. The average time required for the injection of 1000 cubic centimeters was 95 minutes; the shortest time being 43 minutes and the longest time being 149 minutes. The average rate of injection was approximately 10.5 cubic centimeters per minute or about 140 drops per minute. This rate would be equivalent to the administration of approximately 0.0655 grams of nitrogen equivalent to 0.63 grams protein digest per minute or approximately 37.8 grams of protein digest per hour. We have found that the giving of 100 cubic centimeters of solution at a rate less than 10 cubic centimeters per minute results in a moderate amount of physical discomfort to the patient because of the length of time required for the administration.

TABLE II.—REACTIONS

Types of reactions	*No. of reactions*
Type 1: Systematic	
Face flushed	
Feeling of warmth	2 (same patient)
Nausea	
Vomiting	
Type 2: Pyrogenic	
Shaking chill	
Slight elevation in temperature	
Change in pulse rate	5 (4 patients)

Reactions. In 200 consecutive intravenous infusions of the protein digest solution there were 7 reactions equivalent to 3.5 per cent. These reactions are classified in Table II.

A detailed analysis of the reactions follows:

Type 1. Reaction 1. The patient was a white female who had a duodenal obstruction caused by a safety pin. The protein digest solution (Batch No. BW51C), was given on the first postoperative day. The injection was started at a rate of 160 drops per minute. After receiving 300 cubic centimeters of the solution, the patient complained of nausea and a feeling of warmth. Her face was flushed and her skin was rather warm. The rate was decreased to 120 drops per minute and the symptoms subsided. At 400 cubic centimeters the patient vomited. However, she had been vomiting during the morning prior to the administration of the protein digest. This vomiting was not forcible but was characteristic of the type frequently seen after operation. The injection was continued until 500 cubic centimeters had been given. Throughout the last 100 cubic centimeters, there were no objective manifestations in the patient.

Type 1. Reaction 2. This reaction occurred on the following day in the same patient. The solution was from the same batch (No. BW51C) used on the previous day. The fluid was started at 160 drops per minute. After 150 cubic centimeters had been administered, the patient complained of feeling hot. When the rate was slowed to 120 drops per minute, the symptoms decreased somewhat but not completely. She vomited after 250 cubic centimeters had been given, but the injection was not stopped and was allowed to flow at a rate of 120 drops per minute with very little discomfort to the patient. As on the previous day, the patient had been vomiting prior to the intravenous injection.

Type 2. Reaction 1. This patient was a colored male who had a right inguinal herniorrhaphy. The protein digest was given to him on the second postoperative day, and was taken from Batch No. BW61C. The injection was started at the rate of 160 drops per minute and after receiving 300 cubic centimeters the patient complained of numbness in the arm being used. He then developed a shaking chill which lasted about 15 minutes. The fluid was not discontinued and the remaining 200 cubic centimeters

of solution in the bottle was given. At no time did the patient complain of feeling warm or was there any change in the appearance of the skin. There was no change in temperature. This patient was extremely apprehensive about receiving fluids intravenously.

Type 2. Reaction 2. This colored patient had been subjected to an inguinal herniorrhaphy on the same day as the patient in Reaction 1. He was in the same room with the latter and saw him have the chill. He was given the solution from Batch BW61C, the initial rate being 160 drops per minute. After receiving 450 cubic centimeters a chill developed. The injection was stopped for a few minutes and then restarted at 160 drops per minute until 500 cubic centimeters had been given. The chill lasted only a few minutes and there was no change in temperature. There was no actual shaking but only a feeling of chilliness. This patient had become very nervous after seeing the other patient experience the reaction.

Type 2. Reaction 3. This patient was an elderly white female who was critically ill with severe hypoproteinemia, edema, and a papillary cystadenocarcinoma with metastasis in the abdominal cavity. The first infusion of the protein digest solution from Batch No. 102 was given at 130 drops per minute and 1 liter was injected. Forty minutes after the infusion had been completed, the patient had a shaking chill which lasted about 10 minutes. There was a rise in temperature from normal to 101 degrees. She vomited all day but had been vomiting before the infusion. This patient received 10 other infusions of 1 liter each at the same rate and from the same batch, No. 102, of material on 10 consecutive days without showing any further reactions.

Type 2. Reaction 4. This was a colored female with a carcinoma of the descending colon with obstruction. A colostomy had been performed. Practically no food could be taken by the oral route. She was given numerous infusions of the protein digest solution. A reaction occurred with the twelfth consecutive infusion of 1000 cubic centimeters of solution from Batch No. 102. The patient was critically ill at the time. The injection was started at the rate of 160 drops per minute and after receiving 500 cubic centimeters, the patient complained of feeling chilly. The chill lasted for nearly an hour, but the severity decreased a great deal during the last 45 minutes. Throughout the chill and for some time after, the patient was given another 500 cubic centimeters of the protein digest solution (No. 102) at 60 to 80 drops per minute. At the end of the infusion the patient felt normal and there was no further reaction. There was no change in the color or warmth of the skin throughout the reaction. The same tube and needle set was used throughout the injection of 1000 cubic centimeters of solution.

Type 2. Reaction 5. This reaction occurred in the same patient as described in Reaction 4. The solution used was also from Batch No. 102. The injection was started at 140 drops per minute. After having received 450 cubic centimeters, the patient began to have a rather severe chill and the pulse rose from 98 to 125. The infusion was then stopped. The chill lasted 45 minutes. At the end of the chill another 500 cubic centimeters of the same lot of solution was given at the rate of 140 drops per minute, a second tube and needle set being used. There was no reaction with the second 500 cubic centimeters. The patient received 8 other 1000 cubic centimeters infusions of the same lot of material without reaction.

In all there were 7 reactions in 200 consecutive infusions of the protein digest solution. The first two reactions on one patient we have classified as being due to substances present in the preparation which caused a vascular reaction with flushing of the skin, a sense of warmth, and nausea with vomiting. However, since this patient had been vomiting prior to the intravenous administration of the protein digest solution there is some doubt as to whether the vomiting may be attributed to the solution. As has been noted, the vomiting was characteristic of that frequently seen after operation. There were 34 other infusions with the same material in different patients at rates varying between 160 and 120 drops per minute with no reactions.

Reactions of type 2 including reactions 1 to 5 were due chiefly to pyrogenic substances present in the tube and needle set, and were not inherent in the solution used. It will be noted that in all these reactions the patients experienced chills. There was only an occasional associated change in temperature and pulse rate. In no instance in this type of reaction was there any flushing of the skin, nausea, a feeling of warmth, or vomiting which could be attributed to the solution as in reactions of type 1. The statement that the pyrogenic reaction was undoubtedly due to an improperly prepared tube and needle set seems to be borne out.

In reaction 3, type 2 it will be noted that this patient subsequently received 10 other infusions on 10 consecutive days without showing reactions. A similar explanation may be given for the reaction experience in reaction 4, type 2. The fact that the same set was used for the administration of the second 500 cubic centimeters infusion which was given without reaction would indicate that the first lot of 500 cubic centimeters had washed out the pyrogenic materials from the tube and needle set.

In reaction 5, it is clearly shown that the pyrogenic reaction was due to the improperly prepared tube and needle set, since the second lot of 500 cubic centimeters of the same batch was given at the same rate without reaction, when a second tube and needle set were used. Subsequently the patient received 8 other infusions of the same lot of material without any reaction.

During the entire study close observation of the local reaction resulting from the intravenous use of the protein digest solution has never revealed any acute thrombophlebitis. We have noticed that after many infusions in the same arm there was a gradual increase of thrombosis in these veins. However, the same veins were also used for the infusions of other parenteral fluids such as glucose and normal saline solutions. In one case, there was an extravasation of protein digest solu-

tion into the subcutaneous tissue of the elbow in a patient who accidentally pulled the needle out of the vein. The patient complained of a burning sensation at the site but necrosis did not follow.

If we are justified in classifying the 5 reactions of type 2 as being due to pyrogenic substances, and if we assume that the 2 reactions described as being of type 1 were due to substances present in the protein digest solution, the actual reaction incidence would be equivalent to 1.0 per cent.

THE NEED OF PROTEINS AFTER OPERATION

Under normal living conditions, an individual maintains a positive protein balance and stores a reserve of protein which is available for increased metabolism when such a demand arises. Many of the hormones and enzymes have their origin from proteins so that both in health and in disease a certain reserve is essential.

During many diseases there may be an acceleration of the protein metabolism and consequently, the protein is used more rapidly than it is elaborated. This negative balance draws upon the reserve, the tissue, and the plasma proteins, and may if persistent, produce a marked tissue protein deficiency and finally a hypoproteinemia. Madden and Whipple have shown that "a dynamic equilibrium exists between plasma and tissue proteins and that a fall in plasma proteins only occurs after the tissue proteins have been used. Consequently, a significant drop in plasma proteins leaves no room for doubt that the tissue proteins have suffered a like fate." Elman and his associates have estimated, and only after numerous experiments, that for every gram of plasma albumin that is consumed, 30 grams of tissue proteins have been appropriated. Whipple also says that "the plasma proteins take an active part in the internal protein metabolism of the body, that they are built up rapidly, used in the body economy freely, and serve to supply practically all of the protein requirements of the cells of the body."

Patients who undergo surgical operations have a deranged protein balance. This is best explained by these facts: (1) they have a limited and inadequate protein intake; in fact, there is usually a direct relationship between the inadequate intake and the extent of the operation. It may be well said that the more extensive the operation, the more inadequate is the protein diet. Many patients having major intestinal operations are practically starved for 3 to 4 days before operation and for 4 to 10 days after operation. (2) Surgical patients also have an increased protein metabolism. Clinically, this has been demonstrated by the increased nitrogen loss in the urine. Cuthbertson and Brunschwig have noted this condition. We have also found the same excess protein loss.

In a study of uncomplicated cases of inguinal hernioplasties, one of the simple types of major operations, we found that all of them were in negative nitrogen balance postoperatively when given the accepted routine care and nourishment. The average protein deficit for these patients for the first 7 postoperative days was 70.83 grams of nitrogen or 442.68 grams of protein. The greatest deficit occurred during the first 4 days. This protein deficit is frequently reflected in the blood. Meyer and Kozoll report that there is a 5 per cent drop in the average total plasma proteins in surgical patients after operation. Casten, Bodenheimer, and Barcham report a 0.5 gram drop or more in the total proteins in 68.9 per cent of major abdominal operations.

There are many reports in the literature of the incidence of hypoproteinemia occurring before and after operation in surgical patients. Meyer and Kozoll showed an incidence of hypoproteinemia of 22.3 per cent in general surgical patients before operation. We found an incidence of 10 per cent at the Gallinger Municipal Hospital. Ariel and associates (1, 2, 3) found preoperative hypoproteinemia in 59 per cent of the cases of gastric carcinoma, 36 per cent in carcinoma of the colon and rectum and 33 per cent in benign gastrointestinal diseases. The same group found that the incidence of hypoproteinemia increases postoperatively. This is represented by the following figures: 86 per cent of the patients with carcinoma of the colon and the rectum had hypoproteinemia postoperatively, 87 per cent of the cases of carcinoma of the gastrointestinal tract and 44 per cent of the benign gastrointestinal diseases.

In view of all of this evidence, it certainly seems logical to try to fortify surgical patients to decrease this protein deficit. This we have tried by the use of blood, plasma, saline, and glucose solutions. While it is possible to maintain a satisfactory protein balance with blood and plasma, the difficulty of obtaining a sufficient quantity and the expense has almost prohibited this to the average patient. For example, 500 cubic centimeters of plasma contains approximately 30 grams of protein which is only half of the average daily requirements of a healthy individual. In order to maintain nitrogen balance after operation, patients frequently require 70 grams or more of protein every 24 hours to satisfy this need. If we can supply this demand by an

assimilable and usable group of amino acids or protein digest solution that can be given parenterally without serious reaction and without great expense, we have succeeded in solving a vexatious problem.

We have used a protein digest solution that fulfills these requirements, we believe. The following few cases are representative of the results we have obtained. More complete reports of this work will appear in forthcoming publications.

CASE 1. A colored female was admitted with chronic cholecystitis. A cholecystectomy and appendectomy was performed. Postoperatively, patient was given the usual clear liquids for the first 3 days, and then soft diet for the next 4 days. In addition to this, 1000 cubic centimeters of protein digest was given daily to supply as a supplement to protein which was not present in the food. The following figures represent the end-results in the protein metabolism for 7 days.

Total intake		Total output	Deficit
Nitrogen-diet	6.4		
Nitrogen-vein protein digest	43.75		
Total	50.15	69.75	19.60

The striking part of the clinical picture postoperatively was a sense of comfort and well being that the patient exhibited throughout. Had this patient only been treated in the usual manner without parenteral proteins, her deficit would have been 63.35 grams nitrogen or 396 grams of protein; whereas with the use of protein digest the deficit was 122.7 grams of protein, a difference of 274 grams of protein. The blood proteins showed a slight decrease during the first 4 days with a gradual return of slightly above the original level on the seventh postoperative day. In fact, if the hematocrit is taken into consideration there was an actual increase of 0.87 grams of protein per 100 cubic centimeters of plasma during this study. The following figures show the hematocrit and blood protein levels for each day.

Blood Protein Determinations

Days after operation	Hematocrit per cent	Total protein gm.
Operation	47	7.27
1st	43	6.72
2nd	41	6.63
3rd	41	6.85
4th	41	6.95
5th	41	6.99
6th	41	7.16
7th	42	7.5

This case exemplifies the all important *sparing action* of parenteral proteins in the postoperative management of surgical cases.

CASE 2. A colored male, age 43 years, had symptoms of partial intestinal obstruction for 3 weeks previous to this operation. The eating of solid foods caused the patient to become distended and to vomit. It was thought that he had a small bowel tumor. Gastrointestinal studies were only suggestive of an obstruction. An exploratory laparotomy was performed and no tumor was found; however, there were some adhesions between three loops of ileum with slight distention of the bowel proximal to this point. An appendectomy with lysis of adhesions was the operation performed. Postoperatively for the first 3 days, the patient was moderately distended and on the fourth postoperative day active peristalsis had recurred and the convalescence was completely uneventful from this point. The patient received no solid foods for the first 7 days. The diet consisted of water for the first 3 days and then clear liquids for the next 4 days. On the 8th postoperative day the patient was placed on a soft diet and subsequently on a regular diet. Throughout the first 7 days, parenteral fluids, including glucose, saline solutions, and 1000 cubic centimeters of protein digest were administered daily. The following table shows the nitrogen metabolism studies during this period:

Days after operation	Total intake gm. N. by vein protein digest	Total output gm. N.	Difference	Total protein	Albumen	Glob.
Operation	6.25	8.05	−1.80	6.26	3.20	3.06
1	6.25	10.58	−4.33	6.36	3.05	3.31
2	6.25	6.90	−0.65			
3	6.25	7.83	−1.58	6.50		
4	6.25	6.96	−0.71	6.70		
5	6.25	6.00	+0.25	6.20		
6	6.25	8.80	−2.55			
7	9.37	7.60	+1.77	6.25	3.45	2.81
	53.12	62.72	−9.60			

On the 5th and 7th postoperative days, positive nitrogen balance was achieved. The total deficit of 9.60 grams of nitrogen or 51 grams of protein is indeed a small figure as compared to the 392 grams of protein the patient would have lost if he had not received parenteral proteins. We believe that the postoperative course was greatly influenced by the use of protein digest. The parenteral use of protein aids in reducing the postoperative nitrogen loss. This patient, as well as the one in Case 1, had a general feeling of well being postoperatively far beyond that which one sees in a good postoperative convalescence.

SUMMARY AND CONCLUSIONS

1. A protein digest solution, prepared from an enzymatic digest of a mammalian protein and which is pyrogen free, heat sterilized, and contains at least 50 per cent of the total nitrogen in the form of α amino nitrogen, has been administered to a group of patients by means of intravenous injections.

2. The average rate of solution administration used was 10.5 cubic centimeters per minute which is equivalent to approximately 140 drops per minute.

3. In 200 consecutive intravenous injections of the protein digest solution in 49 patients, there were 7 reactions or an overall reaction incidence of 3.5 per cent. Two of these reactions, or 1 per cent, experienced by the same patient, have been classi-

fied as systemic reactions or 2.5 per cent occurring in 4 different patients have been attributed to pyrogenic substances present in the tube and needle set. A discussion of the reactions is presented.

4. No acute thrombophlebitis was observed as being due to the injection of the protein digest solution.

5. The protein deficit which exists in surgical patients after operation has been performed is pointed out; the value of the use of a digestible and assimilable protein intravenously in order to supply this protein deficit so as to avoid a negative protein balance which drains the body and plasma proteins is discussed. A few cases are presented which exemplify the efficacy of this protein digest.

6. This protein digest solution may be safely used in critically ill surgical patients as a simple method of supplying a source of parenteral protein.

7. It is possible that in some cases, the addition of vitamins, glucose, and inorganic salts may be advantageous.

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PRACTICAL CONSIDERATIONS IN DEFINITIVE AMPUTATION SURGERY

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IN this discussion we wish to emphasize certain technical procedures which have been found helpful in securing painless, well shaped, useful stumps in lower leg, thigh, forearm, and arm amputations. Specialized technical procedures, such as fusion of the fibula to the tibia, lengthening operations, and removal of the fibula, will not be considered. Also, for the sake of simplicity, the well known and often discussed amputations—Lisfranc, Chopart, Pirogoff, Syme, Callander, disarticulation, and Gritti Stokes—will be omitted.

When the dressings are removed from patients with amputations who arrive for definitive surgery at a general hospital and a well performed guillotine amputation with adequate skin traction is disclosed, there is a silent word of thanks to the surgeons at the Front because the problem of definitive surgery has been greatly facilitated and the success or failure of securing the best possible stump rests firmly upon us.

An amputee is keenly interested in a good result. This type of surgery is always under the close surveillance of the patient himself. He compares his stump as to comfort, appearance, and function with those of other similar cases, and sets up his own standard for a good result which stands little correction. It is interesting to note that many, within a few hours after they arrive at the general hospital, have by some method found their way to the brace shop and the physical therapy department, have talked with other patients in similar circumstances, and have formulated definite opinions about the "amputation center" in general. Therefore, the surgeon must not only obtain the maximum in shape and function for the prosthesis maker and for his own personal satisfaction, but for the general morale on his service.

GENERAL CONSIDERATIONS

The anesthesia used at Bushnell General Hospital for lower extremity amputation surgery has generally been spinal; for forearms, brachial blocks; for upper arms, inhalation or intravenous pentothal sodium. It is essential to select an anesthesia that allows sufficient time for all the intricate details, including absolute hemostasis.

Whenever possible, the surgery is done with a tourniquet in place until the amputation has been performed and flaps have been fashioned ready for closure. The extremity is elevated and bled by tightly applying ace bandages from the distal end to the site selected for the tourniquet. The tourniquet itself may consist of the usual rubber commercial type, multiple ace bandages (3) one over the other or in upper extremities a blood pressure cuff with a superimposed ace bandage.

Nerves are treated with 20 per cent formalin,[1] tinted with methylene blue, injected between two ligatures approximately 1 centimeter apart which insures an equal diffusion of the solution throughout all nerve fibers in this segment. After a few seconds, the proximal ligature is removed and the nerve transected just distal to the remaining ligature, care being taken that the nerve end is high in normal tissue away from the line of closure. It is realized that the various methods of treating these sectioned nerves are controversial. Injection of 95 per cent alcohol is utilized by many surgeons with good success and it is highly possible that the many advocates of simple nerve division without ligation or any injection may prove to have the best method.

The suture material has been cotton, Nos. 40, 80 for deep fascial approximation, 120 for ties and subcutaneous and C-Deknatel silk for skin closure. All stumps are closed snugly without drainage[1].

PREPARATION

Extremities to be revised or reamputated should be free of open draining wounds or granulating areas[1] except in a few instances in which the selected site for reamputation is well away from the open area. The waiting period after the stump has become dry is in proportion to: (1) the length of time the stump had drained, (2) the depth of the wound which was draining, and (3) the type of organisms that were present during the healing period. For example, a guillotined

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[1]This is the practice at Bushnell General Hospital and must not be interpreted to be that common to all Army amputation centers.

stump with adequate skin traction that heals rapidly and becomes dry in 4 to 8 weeks may be operated upon in 14 to 21 days after becoming dry, provided the scar can be removed *en bloc*. An indolent healing amputation that has contained sinus tracts, ring sequestra, foreign material, organisms of high virulence, etc. and in which revision or reamputation is contemplated in the immediate vicinity of the scarred end should remain dry 30 to 60 days before definitive surgery is carried out. Often, if we wish to close a granulating stump rapidly to shorten the waiting period, our plastic surgeons have been prevailed upon to place several pinch grafts[1] on the open end to speed the healing time. In some instances the reapplication of skin traction has hastened the period of healing as well as relaxed the skin for revisions near the guillotined end. Attempts to hasten matters by reamputating before complete closure have proved unwise in our hands.[1] Certainly the methods advocated in this paper are not all applicable if reamputations are done in the presence of such likelihood of contamination.

At present we are treating, with intramuscular injections of 15,000 to 25,000 units of penicillin every 3 hours, a comparative group of patients from whose wounds cultures show penicillin sensitive organisms. The operation is then done as soon as the wound becomes dry or the culture from the wound sterile (usually in about 5 to 7 days) and penicillin therapy is continued for 7 to 10 days after operation. Results of this method are not conclusive at this time.

Except in the penicillin group, all patients are prepared for 2 or 3 days with sulfadiazine, grams 1, given once every 4 hours and a booster dose of tetanus toxoid before surgery and sulfadiazine continued after operation for 10 to 15 days unless contraindicated. The amputated member is shaved, cleaned with green soap, alcohol, ether, and wrapped in sterile dressings the afternoon of the day preceding the operation.

AMPUTATIONS BELOW THE KNEE

If a guillotine amputation has been done in the lower third of the leg, a site for the level of division of the tibia is selected between 5 and 7 inches from the tibial table. This level is marked around the leg on the overlying skin, with methylene blue. Our desire is to have the line of skin closure posterior to center. Flaps are accurately measured by first estimating the anteroposterior diameter of the leg at the level selected for amputation of the tibia. This diameter can be measured by placing a short rule by the leg and sighting, or it can be more accurately determined by measuring the circumference of the leg and dividing by three. We utilize two-thirds of this diameter for the length of the anterior flap and one-third for the posterior. A methylene blue mark is therefore made on the skin anteriorly below the level for amputation of the tibia at a distance two-thirds of the diameter. Posteriorly, the mark is made at a distance one-third of the diameter. An anterior and posterior skin flap is then plotted with methylene blue from these established levels. Since the skin will retract when the anterior flap is cut, the distance from the bone level selected for amputation to the distal part of the anterior flap is measured accurately, and the tibia is scored at the distal level when the skin incision is first started anteriorly. After the skin flap has been reflected, this measurement can then be plotted on the tibia itself and the site of amputation permanently established with a chisel mark. The establishment of a stationary mark for amputation for reference in fashioning skin and fascial flaps as well as for trimming muscles is important and time saving as the shifting of skin and other structures due to retraction or steadying of the limb by an assistant may cause the surgeon to section the tibia at a higher or lower level than anticipated thus necessitating a revision of his planned procedure.

A long posterior fascial flap is then fashioned and cut except in its distal posterior aspect, the medial and lateral portions being dissected free so they may be retracted to avoid injury when the amputation knife is carried under the tibia and fibula. A ½ inch anterior fascial collar is prepared, care being taken to separate the fascia where it is closely adherent to the periosteum of the tibia without lifting the tibial periosteum. The fibula is approached through the posterior lateral muscular raphe between the peroneus longus and the soleus and dissected free of its attachments extraperiosteally to a level approximately 1 inch shorter than the selected site of amputation. The anterior tibial artery and its plexus of veins should be identified and ligated through this approach, thus avoiding unnecessary bleeding when the tourniquet is released. At this level the periosteum is ringed and stripped distally, a Gigli saw is passed around the fibula, and the bone cut transversely about ⅛ inch distal to the proximal periosteum. We do not remove the muscles at the level of the fibular amputation but divide them at the level selected for the amputation of the tibia. This muscular tissue fills the defect left by the removed fibula and keeps the stump end straight (Fig. 1).

[1]This is the practice at Bushnell General Hospital and must not be interpreted to be that common to all Army amputation centers.

The posterior fascial flap is made very long and free of attached muscle below the level of division of the tibia. In forming this fascial flap, we rotate the fibula anteriorly to the level of the tibia, insert the blade just behind the bones, divide all muscle fibers perpendicularly, taking care to avoid any incision into the fascia. The knife is then turned parallel to the posterior border of the tibia carried distally anterior to the gastrocnemius fascia and cut across at the desired low level. The periosteum of the tibia is rimmed with a knife at the site of amputation including the anterior bevel and stripped distally. The tibia is sawed about ¼ inch distal to the periosteal collar. The distal segment is discarded and the vessels and nerves can be plainly seen and ligated. The gastrocnemius fascia is cleaned of any remaining muscle. We wish to stress the point that in *not* carrying the line of dissection of the posterior muscles obliquely downward, resultant redundancy in the posterior aspect of the stump is avoided (Fig. 1).

With the hand placed under the leg near the amputated end and with slight pressure upward, a bulge of gastrocnemius muscle will be seen on the medial aspect of the tibia. A wedge of this muscle is removed to insure a straight stump (Fig. 1). The tourniquet is now removed and absolute hemostasis is established. Fascial flaps and skin are then closed under slight tension. We have adopted a dressing consisting of voluminous gauze fluffs or mechanics' waste held by an ace bandage or sheet wadding and a light plaster cast applied over all to the upper third of the thigh with the knee in full extension. Twenty-four to 48 hours later the cast is bivalved, and the lower half is used as a posterior mold until the incision is healed (Figs. 2 and 3).

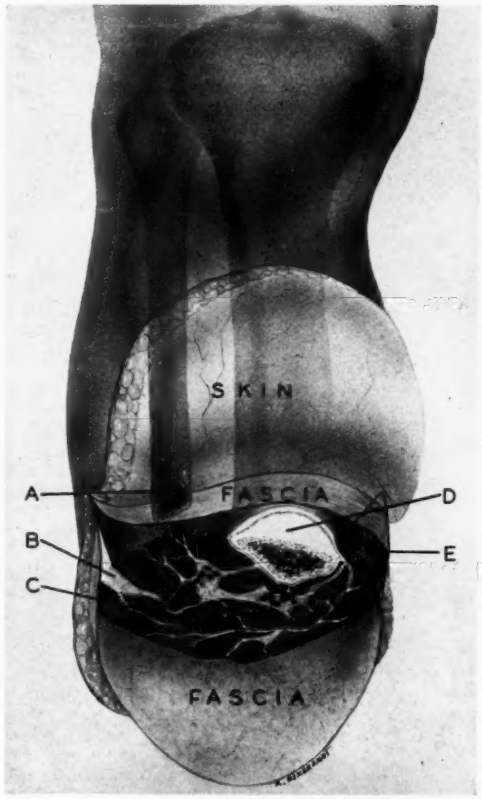

Fig. 1. *A* shows the fibula which was approached through the intermuscular raphe *B* and cut about 1 inch shorter than the tibia. *C* illustrates the muscles cut transversely at the level of amputation. *D* represents the beveled tibia. *E* denotes the segment of gastrocnemius muscle to be removed before closure.

AMPUTATIONS OF THE MIDDLE AND LOWER THIRD OF THE THIGH

In considering definitive surgery on guillotined thighs it is of prime importance to save as much length as possible. Re-establishment of skin traction 5 days before surgery will often forestall shortening of the femur. The scar is removed *en bloc* and if severe spurring is present at the femoral end, a distal segment of the bone is removed with the scar. The skin flaps are planned and marked much the same as in lower leg amputations with a long anterior and short posterior flap. The skin is reflected, and anterior and posterior fascial flaps prepared by utilizing all nonscarred fascia. The bone end is treated by removing a ¼ inch periosteal cuff or if it is well covered with deep fascia and no spurring has occurred it is not disturbed. A generous wedge of muscle is removed from the region of the vastus medialis and vastus lateralis and the quadriceps femoris is thinned near the amputated end of the femur. No muscular attachments should be disturbed proximal to the femoral end. The removal of these segments of redundant muscle tapers the stump, facilitates proper shrinkage, makes for better fitting prostheses, and often supplies the needed fascia and skin necessary to forego shortening the femur. Here again absolute hemostasis is required before closing the wound. In approximating the fascial and skin flaps it is well to put slight transverse tension on the lower flaps to avoid longitudinal folds in the posterior thigh when shrinkage of the stump occurs. The initial postoperative dressing consists usually of

Fig. 2. Left stump is more satisfactory than right. The undesirable curve of the right stump is due to (1) the removal of lateral musculature below the divided fibula and (2) the need of removal of a medial wedge of gastrocnemius muscle.

voluminous gauze fluffs or mechanics' waste, ace bandages, and a single light plaster hip spica with

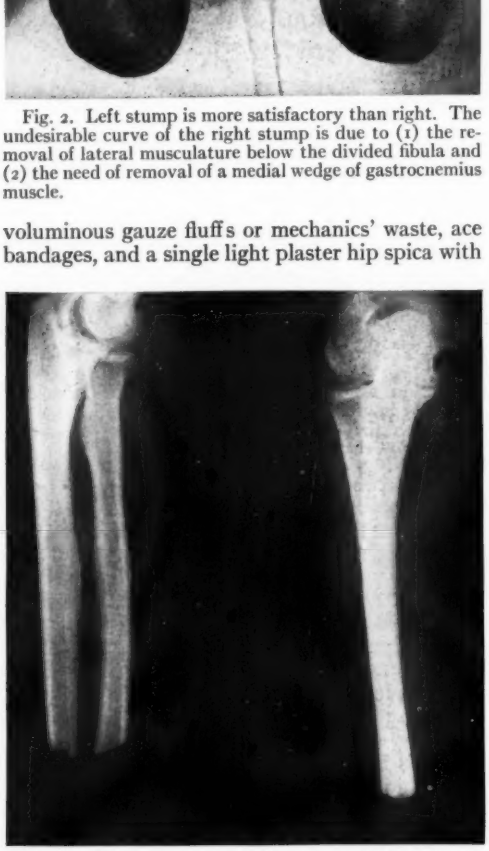

Fig. 4. The radius and ulna have been obliquely cut to aid in rounding the stump end of the forearm.

Fig. 3. Left stump more satisfactory than right. Excess muscle posteriorly in the right stump resulted in a redundancy of soft tissue and at the same time undesirable tension on the skin scar when a prosthesis is worn. Blood supply was inferior, blebs formed in the scar, the stump was tender, and there was a delay in using a prosthesis comfortably on the right.

the stump in a neutral position or in slight abduction and the dressing is left in place 10 days. When closure has been made under tension, skin traction is applied with stockinette over ace adherent.

AMPUTATIONS OF THE FOREARM

If the guillotine amputation is at or near the wrist, the site of reamputation is selected where the muscular portion of the forearm tapers to form the distal tendinous segment and wrist. An equal anterior and posterior skin flap is marked with methylene blue. At the angle over the radius, the skin is opened and a chisel mark is made in the radius to establish the site of amputation. This mark will be found very useful during the various stages in the reamputation. Both skin flaps are cut and reflected and the distal skin is reflected as well to facilitate the fashioning of fascial flaps longer than the skin. The fascia is reflected only to the marked site of amputation. Nerves and vessels are identified, ligated, and treated as described. The muscles are cut transversely at the site of amputation; nothing is disturbed proximal to this point except the nerves. The periosteum of the radius and ulna is cut obliquely and stripped distally. With the two bones held parallel, they are sawed obliquely[1] about ⅛ inch distal to the periosteum and the edges are filed (Fig. 4). The tourniquet is removed and all bleeding points are ligated. Overlapping of the fascial flaps under tension has proved beneficial because it affords better covering to the bone ends and does not

[1]This is the practice at Bushnell General Hospital and must not be interpreted to be that common to all Army amputation centers.

place the line of closure immediately under the line of skin closure, thus giving freely movable skin over the stump end. The stump is lightly dressed, wrapped snugly to the elbow with two ace bandages and kept elevated. The ace bandages are loosened in 24 hours to relieve the pressure under which they were applied.

AMPUTATIONS ABOVE THE ELBOW

In revisions or reamputations of the upper arm as much length as possible is sought, the supracondylar amputation being ideal. Here again, necessary skin may often be obtained by the use of skin traction a few days preceding surgery. Scar tissue of the guillotined end is removed *en bloc* and the bone end treated much the same as in thigh amputations. Equal skin flaps are dissected or such skin as is available to maintain length since the placing of the scar is not of prime importance on the nonweight bearing stumps except to avoid a scar on the anterior surface of the upper arm where slight pressure will be exerted in lifting the prosthesis. One point has come to our attention that is helpful in securing a good upper arm stump. It is customary to do the surgery with the arm abducted on an operating board. If the flaps are closed in the usual manner with the arm in this position, it will be found later that with the arm held at the side there is a redundancy at the stump end. Therefore, before closure of the fascial and skin flaps it is wise to place the arm first at the patient's side and then in abduction to shoulder level, to estimate properly the degree of tension at which to close. The same is true if a blood pressure cuff is used as a tourniquet. The cuff should be entirely removed, not just deflated, so that the tissues can assume their normal position before the tension of the flaps is estimated. The immediate postoperative dressing consists of a light gauze fluff over the end followed by tight ace bandaging to be released and reapplied in 24 hours.

SUMMARY

1. Definitive amputation surgery of the lower leg, thigh, forearm, and arm at ideal levels has been discussed.

2. The period from which the stump first becomes dry to the definitive surgery is in proportion to the length of time the stump has drained and the virulence of the organisms that have been present.

3. A permanent stationary mark on the bone at the amputation site for reference during the operation materially aids in correct fashioning of skin, fascia, and muscle for closure.

4. To avoid posterior redundancy and insure a straight stump in below the knee amputations, the posterior muscles should be sectioned transversely at the site of amputation, the lateral muscles should be left in place from the amputated end of the fibula to the level of the tibial amputation and a wedge of gastrocnemius muscle should be removed at the medial and distal aspect of the tibia.

5. In thigh amputations a medial and lateral wedge of muscle as well as tapering of the quadriceps femoris aids in preventing redundancy and obtaining a conical stump.

6. Beveling of the radius and ulna, imbricating the fascia, and disturbing no muscular attachments proximal to the amputation site facilitate the fashioning of a better appearing and functioning forearm stump.

7. The changing of the position of the arm from abduction to the neutral position at the patient's side before closure of fascia and skin will facilitate the correct estimation as to the tension at which to close the amputated end.

CONSERVATIVE MANAGEMENT OF ADOLESCENT SLIPPING OF THE CAPITAL FEMORAL EPIPHYSIS

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THE divergence of opinion on management of adolescent slipping of the capital femoral epiphysis in its various stages is evidence of limited success in the treatment of this condition. Many unsatisfactory functional results have followed currently popular methods of treatment.

This report is a review of 44 cases in which treatment was directed toward restoration of function. Trauma to the epiphysis by operation or manipulation was avoided when possible.

Recognition of early symptoms, signs, and roentgenographic findings has led to earlier diagnosis and treatment when epiphyseal displacement is minimal and no significant functional impairment present. Ossification of the epiphyseal cartilage growth disc in such cases is an accepted criterion of successful treatment if further displacement is to be prevented (9, 27, 31). Various surgical procedures have been advocated to hasten ossification of the growth disc or to fix the epiphysis to the femoral neck until bony union occurs (9, 14, 32). In the cases reported here closure of the epiphysis occurred within 3 to 12 months without additional trauma of drilling, etc. The longer disability occasioned by conservative treatment was of little economic significance in most instances. It is believed that the risk of damage to the blood supply to the epiphysis following operations outweighs the advantage of reducing the period of disability when nonoperative methods accomplish the same result over a slightly longer period.

With moderate displacement of the epiphysis, without bony union, discussion has centered chiefly on the indications for and against manipulative or operative methods of replacement. The question of the necessity or advisability of accurate replacement has not been settled. The general belief is that disabling arthritis is inevitable after the third decade if the deformity is allowed to persist, and that accurate replacement of the epiphysis will prevent this late sequela. There is no evidence that the first contention is generally true, and reports in the literature show a high incidence of degenerative arthritis after several years in patients in whom replacement by manipulation or operation has been done (4, 9).

Manipulative attempts at replacement of an epiphysis which has not yet united have failed in most instances (7, 9, 13, 15, 19, 22, 23, 25, 26, 27, 28, 30) to bring about any change in the anatomical relationship of the epiphysis with the neck unless the neck is fractured below the zone through which slipping takes place. The anatomical basis for this difficulty in replacing the epiphysis has been described by Wardle. Actually much depends on the rate of slipping. When acute displacement is present replacement is readily accomplished. The slower the rate, and the longer the displacement has existed, the greater the difficulty of replacement. Correction of the limb deformity in long standing cases, without actual fracture of the neck, is usually at the expense of the capsule and ligamentum teres which may be badly torn. Many cases of progressive loss of motion and pain in the hip have been reported following this procedure (3, 4, 9, 15, 21, 22, 23, 24, 25, 31). Waldenstrom (27), and McMurray have reported aseptic necrosis of the epiphysis in 25 per cent of their patients so treated.

Gradual replacement by prolonged traction in adduction and internal rotation has been shown by Wardle to be successful in a number of cases. However Howorth reported 5 poor functional results in 7 patients treated by strong traction and immobilization. He reported good correction of the upward displacement of the neck in most of the cases, but found that the rotation usually could not be changed. Late irregularity of the shadow of the cortex of the head, irregular ossification of the epiphysis, and thinning of the articular cartilage on the roentgenogram were found in most of his cases.

Operative freeing of an epiphysis which has not united to the neck converts a slowly progressing displacement of the epiphysis into an acute fracture separation. The epiphysis is subjected to the danger of infarction unless the blood vessels in the ligamentum teres or undamaged posterior portion of the visceral capsule furnish adequate nutrition.

Rest has long been known to bring about considerable improvement of function if instituted

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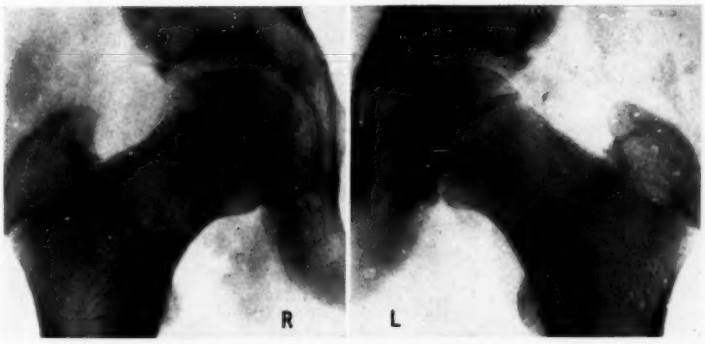

Fig. 1. Case 1. Minimal displacement of the left capital epiphysis. Note signs of impending closure of the right capital epiphyseal growth cartilage.

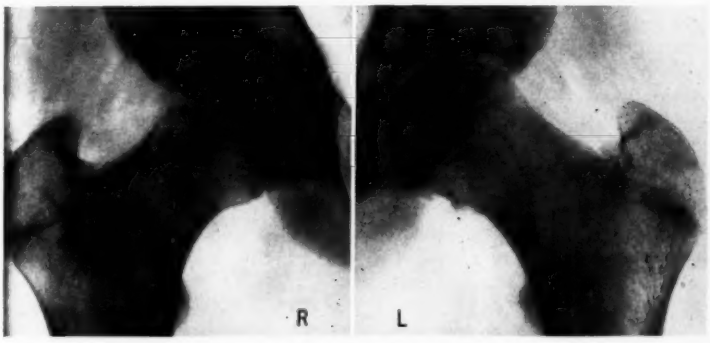

Fig. 2. Case 1. Four and one-half months after onset of treatment. The left epiphyseal growth cartilage is completely ossified. The right is almost obliterated. The left greater trochanter is closing with the capital epiphysis.

during the stage of progressive displacement (8, 12, 15). Unless the anatomical deformity of the head and neck is severe a large component of the limb deformity and loss of function appears to be due to muscle spasm. Treatment by immobilization only was found to leave no significant functional impairment in over 47 per cent of the patients with moderate displacement of the epiphysis, without union, reported here. If the residual anatomical deformity of the epiphysis on the neck impairs abduction and rotation, subtrochanteric osteotomy corrects the limb deformity without endangering the blood supply to the epiphysis.

If the epiphysis is united with the neck when the patient is first seen, it is likewise obvious that reposition by force can only take place following fracture of the neck. In cases of this type surgical reposition can be brought about only by osteotomy of the neck. The coxa vara in such instances has usually been of long standing, and the posteroinferior portion of the capsule has become adapted to the changed position of the head. Thus tension on the capsule following reposition, or injury to this structure when wedge osteotomy is done, may occlude the vessels of the posteroinferior portion of the capsule.

End-result studies 5 to 14 years after surgical reposition or femoral neck osteotomy have shown variable results in patients with moderate displacement with or without bony union. Wilson (30), Ghormley and Fairchild, and Kleinberg and Bochman have reported good results in patients observed over this period. However a review of 87 cases recorded in the literature from 1924 to 1942 (3, 4, 7, 10, 11, 13, 16, 19, 21, 22, 29, 30) does not show encouraging results. Aseptic necrosis of the epiphysis is reported in 13 per cent of the cases following operation, and the reported poor results are over 50 per cent.

Soft parts contracture about the hip plays a significant rôle in preventing correction of the limb deformity after union of a severely displaced epiphysis has occurred. Anatomical replacement cannot be obtained without trauma to these structures. Such trauma predisposes to subsequent loss of motion and interference with the blood supply to the epiphysis. Correction of the limb deformity and realignment of the weight bearing surface of the epiphysis by extracapsular osteotomy has not led to these complications in such cases in this report.

Sudden trauma, superimposed on a slipping capital epiphysis, may result in complete separation. As in adults following fracture of the neck of the femur, the blood supply to the epiphysis may be interrupted at the time of the accident or may be caused by additional trauma after the accident. It is believed advisable in such cases to avoid additional trauma by attempting to bring about reposition through gradual traction, with the limb in abduction and internal rotation. This may be successful if separation has occurred within 4 to 6 weeks. After this period, or if reposition by traction is impossible, surgical reposition and internal fixation of the epiphysis seems indicated.

These facts and principles form the basis of the conservative treatment of 44 cases of slipped femoral epiphysis reported here. These cases have been observed at the University of Chicago Clinics during the past 14 years.

TREATMENT AND RESULTS

Bilateral displacement of the epiphysis was observed in 11 patients, or 25 per cent of the total number. The remaining 33 patients had involvement of one side only. A total of 55 displaced epiphyses were studied. Group I includes 29 hips in which epiphyseal displacement was minimal; in group II are 23 hips in which displacement was moderate; and in group III are 3 hips in which fracture separation of the epiphysis had occurred.

Good results are those with 90 degrees or more of flexion, 30 degrees or more of abduction, internal rotation of 5 to 10 degrees, and not more than 3 centimeters of shortening. Function is normal and painless with all activity. Fair results signify 45 to 90 degrees of flexion, 15 to 30 degrees of abduction, rotation to midposition only, and no pain with ordinary activity. Poor results are those with marked limitation of motion, deformity, or epiphyseal necrosis. Intermittent pain is usual with ordinary activity. Uncertain results include cases followed elsewhere on which follow-up studies were not available. Results are based on examination 2 to 6 years after treatment.

Group I, minimal displacement. Minimal displacement was observed in 29 hips included in group I. Twenty-six of these were treated. Two of the remaining 3 showed osseous union when discovered and required no treatment. The third untreated patient showed roentgenographic evidence of union and aseptic necrosis of the epiphysis on admission. Treatment was directed toward alleviation of symptoms due to this complicating factor.

Two patients were treated by bed rest alone, and closure of the epiphysis occurred without further displacement. This is not an approved method of treatment, however, as progressive displacement may take place under such circumstances. Treatment of the remaining 24 consisted of immobilization of the affected limb in plaster until ossification of the central portion of the epiphyseal growth plate took place. This required from 3 to 9 months. Wide abduction and internal rotation of the limb were considered important factors in removing the shearing stress from the epiphysis during this period. The plaster bandage encased the opposite thigh in abduction to prevent tilting of the pelvis and loss of abduction on the affected side. When bilateral displacement was present both limbs were immobilized in wide abduction and internal rotation. Spasm occasionally prevented attainment of this position. Bed rest for 7 to 10 days usually relieved this difficulty. No attempt was made to alter the position of the epiphysis on the neck.

The following case with minimal displacement exemplifies rapid ossification of the cartilage growth plate following a short period of immobilization alone.

Case 1. C. C., a boy, 15 years and 2 months of age, complained of pain on the inner aspect of the left thigh and knee of 3 months' duration. Pain was present only when he was walking or running. Examination showed a moderately obese boy with small external genitalia and prostate. Pubic and axillary hair was scant. There was 1 centimeter of shortening and limitation of internal rotation of the left leg.

The roentgenogram (Fig. 1) shows slight upward displacement of the neck of the left femur on its epiphysis and the characteristic juxtaepiphyseal zone of osteoporosis. The right hip shows narrowing of the cartilage disc of the capital epiphysis. Sclerosis on both sides of the growth cartilage indicates imminent closure of this epiphysis.

Immobilization of the left leg in abduction and internal rotation for 6 weeks was carried out. This was followed by partial weight bearing with crutches for an additional 2½ months. Four and one-half months after admission he was bearing full weight without support and ossification of the capital epiphyseal growth cartilage was complete (Fig. 2).

At this time closure of the opposite capital epiphysis was nearly complete. Examination 2 years later showed 1 centimeter of shortening of the left leg, normal motion of the hip, and closure of the proximal femoral epiphyses of both sides.

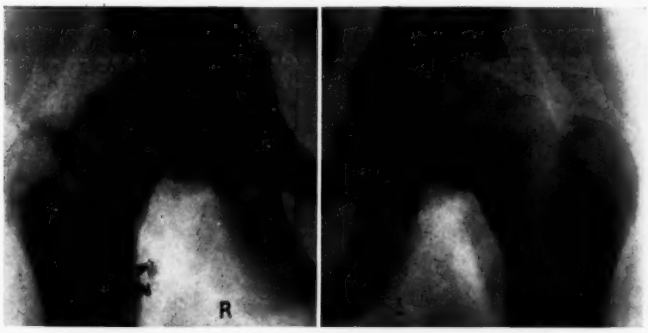

Fig. 3. Case 2. Moderately advanced displacement of both capital epiphyses. Anteversion of the neck is more marked on the right.

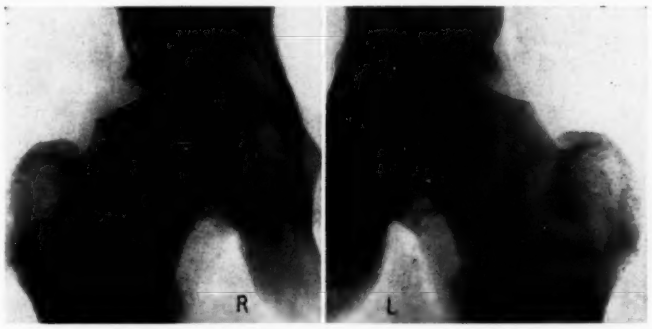

Fig. 4. Case 2. Two and one-half years after admission. There has been no reduction of the displacement. Motion is good, and the gait is normal and painless.

The results in group I are summarized in Table I.

TABLE I.—RESULTS IN 29 CASES IN GROUP I

Treatment	Hips	Good	Fair	Poor	Uncertain
Bed rest	2	2			
Cast	23	21			2
Traction and cast	1			1	
No treatment	3	2		1 (N)	
Total treated	26	23		1	2

(N)=Roentgenographic or pathologic evidence of aseptic necrosis of the epiphysis.

Three of the patients in group I developed slipping while under ambulatory treatment for the same condition on the opposite side. All healed satisfactorily following immobilization. These 3 cases in which crutches or caliper brace were initially used are listed under treatment by cast since bilateral involvement necessitated immobilization of the initially affected limbs which were not healed at the time slipping of the opposite epiphysis occurred.

The 1 poor result following treatment by traction and cast is noteworthy. The growth cartilage ossified as usual, but severe atrophy and progressive loss of motion of the joint occurred. Temporary fibrous ankylosis was the outcome. Identical changes took place in the opposite hip in which epiphyseal displacement was slightly more marked. The cause of this phenomenon is unknown.

Arthroplasty of the hip was performed in the 1 case in group I with necrosis of the epiphysis. The pathologic findings in this case have been reported elsewhere (18).

Residual leg length inequality in cases of this group with unilateral involvement is determined by 2 factors: (1) by the amount of initial upward displacement of the femoral neck on its epiphysis; and (2) by the amount of subsequent growth of

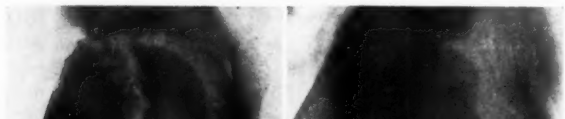

Fig. 5. Case 3. Complete separation of the right capital epiphysis. The roentgenographic density of the epiphysis and shaft is the same.

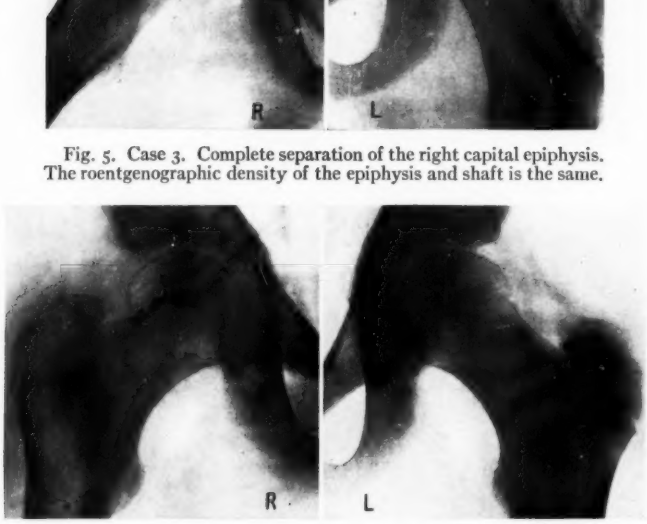

Fig. 6. Case 3. Three and one-half months after admission. Bony union of the epiphysis and neck has occurred. Viability of the epiphysis is indicated by its participation in the disuse atrophy with the shaft.

Fig. 7. Case 3. One year and 6 months after admission. Normal motion and function without pain. Note the intact articular cortex and normal joint space indicating viability of the epiphysis and articular cartilage. The right capital and greater trochanteric epiphyses have closed simultaneously.

the capital and greater trochanteric epiphyses of the unaffected side following premature closure of these epiphyses on the affected side. As previously mentioned, closure of the slipped epiphysis in this group occurred 3 to 9 months after immobilization of the limb. The greater trochanter on the affected side usually closed at the same time or shortly thereafter. The capital and greater

trochanteric epiphyses of the unaffected side closed at the normal time. Only 15 to 17 per cent of the growth of the leg takes place from the proximal end of the femur, and since epiphyseal displacement characteristically takes place near the end of the growth period, growth from the unaffected proximal femoral epiphyses is usually not great. Three centimeters was the maximum limb length discrepancy from growth inequality and displacement in this group. In this 1 instance closure of the opposite epiphyses took place 3 years after closure of the affected epiphyses. The usual limb length difference was 1 to 1.5 centimeters which is of no functional significance.

Reduction of the angle of the neck by overgrowth of the greater trochanter on the affected side is prevented by simultaneous closure of the capital and greater trochanteric epiphyses.

Group II, moderate displacement. Moderately advanced displacement of the epiphysis was observed in 23 hips included in group II. Bony union of the epiphysis was present in 3 cases on admission. The remaining 20 cases were first seen during the period of progressive displacement.

Deformity, limp, and limitation of motion were usually more marked in this group than in group I. Bed rest alone was used with success in 1 case but is not an approved form of treatment. Gradual replacement by strong traction on the limb in abduction and internal rotation was attempted in 2 cases before the limb was immobilized in plaster. Adhesive skin traction for 2 to 3 weeks was used, but in neither case was definite alteration of the position of the epiphysis brought about. In 19 cases plaster immobilization of the limb in abduction and as much internal rotation as was possible without force was carried out. General anesthesia was used in several instances to overcome intractable spasm, but a forceful attempt at replacement of the epiphysis was made in only 1 case. Further correction of the limb deformity could frequently be obtained after 6 to 8 weeks when the first plaster bandage was changed. Plaster immobilization was maintained in such cases for variable periods from 8 weeks to 7 months. Freedom from weight bearing was maintained until osseous union of the epiphysis took place. Restriction of weight bearing with crutches, and frequent roentgenographic examinations were carried out during the early ambulatory period to make certain that healing was functionally sufficient.

The 3 patients showing roentgenographic evidence of bony union of the epiphysis on admission underwent subtrochanteric osteotomy for correction of severe deformity and shortening. Preliminary immobilization is of little value in such cases. Symptoms and deformity had been present for a year or more in all these cases.

Normal function following bilateral moderate displacement of the epiphyses is shown in the following case treated by immobilization alone.

CASE 2. J. G., a boy, 12 years and 5 months of age, was admitted 6 months after onset of pain in the left thigh. Pain in the right thigh had begun 4 months before admission. He had been unable to walk for 10 days because of pain. Examination showed a moderately obese boy. The right leg was in fixed external rotation. Internal rotation of the left leg was markedly limited. Flexion at the hip was limited to 50 degrees on the right side and to 60 degrees on the left. Abduction of either leg beyond 10 degrees was impossible.

The roentgenogram (Fig. 3) shows moderate displacement of both femoral necks on their epiphyses with more marked anteversion of the neck on the right side.

The legs were immobilized in plaster in abduction and neutral rotation after 9 days' bed rest. Immobilization for 7 months was necessary before ossification of both growth cartilages became apparent. This period was followed by weight bearing with crutches for 2 months. Motion improved in both hips during the following year, and examination 2½ years after admission showed a normal gait, normal motion of the hips and knees, and no deformity.

The roentgenogram at this time (Fig. 4) shows closure of both capital and greater trochanteric epiphyses.

TABLE II.—RESULTS IN 23 CASES IN GROUP II

Treatment	Hips	Good	Fair	Poor	Uncertain
Bed rest	1	1			
Cast	15	9	3		3
Traction and cast	2	1		1	
Manipulation and cast	1				1
Splint—cast—osteotomy	1			1 (N)	
Osteotomy	3			3 (N)	
Total treated	23	11	3	5	4

(N)—Roentgenographic or pathologic evidence of aseptic necrosis of the epiphysis.

The results in group II are summarized in Table II.

Function after treatment was normal in 11 cases without bony union in group II. The amount of initial displacement on the roentgenogram was no index to the degree of functional improvement to be expected in these cases.

Attempted replacement of the epiphysis by manipulation in 1 case was unsuccessful. This case could not be followed and the final result is not known.

Epiphyseal necrosis followed progressive displacement while under ambulatory treatment in a caliper brace in 1 case. Collapse of the superior portion of the head required realignment of the

weight bearing surface of the epiphysis by subtrochanteric osteotomy.

The 3 cases in which bony union of the epiphysis was evident on admission showed density contrast between the epiphysis and the shaft, and irregularity of the shadow of the epiphyseal cortex on the roentgenogram. In these cases with aseptic necrosis, improvement of gait, correction of deformity, and partial correction of leg length inequality followed subtrochanteric osteotomy. Persistent intermittent pain with ordinary activity necessitates classification of these cases as poor results in spite of improvement which followed treatment.

Shortening of the affected side of 3 centimeters or less was not found to be of significance. Marked cervical-capital overriding, when present, is of as great importance as the growth arrest in the causation of leg shortening in this group. Another factor, equally important in producing limb length inequality in cases with long standing disability, is inhibition of growth of the epiphyseal cartilages of the tibia and distal end of the femur due to prolonged disuse of the limb. In 1 case showing evidence of bony union and epiphyseal necrosis on admission, displacement on the affected side, continued growth of the unaffected proximal femoral epiphyses, and retardation of growth of the lower femoral and tibial epiphyses on the affected side led to approximately 10 centimeters of shortening of the affected limb. Subtrochanteric osteotomy and a leg lengthening operation were necessary to correct this deformity.

Group III, complete separation of the epiphysis. Complete separation of the epiphysis following trauma was observed in 3 cases in group III. Sudden displacement occurred 2 weeks before admission in 1 case (Case 3). In a second case complete separation occurred following a fall 3 weeks before the patient was first seen, and the third case was referred 13 months after fracture separation of the epiphysis following injury.

Satisfactory reposition of the epiphysis was accomplished by gradual traction in the first case shown here.

CASE 3. E. S., a boy, 12 years and 10 months of age, was admitted 2 weeks after a fall resulting in pain, deformity, and shortening of the right leg. He had complained of mild pain in the right thigh and knee for 2 months before the injury. Examination showed a thin, normally developed male. The right leg was shorter than the left and was externally rotated.

The roentgenogram (Fig. 5) shows complete separation of the right capital epiphysis. The right leg was held in abduction and internal rotation by adhesive skin traction for 26 days. A roentgenogram then showed marked but not complete replacement of the epiphysis. A plaster spica was then applied and was removed 3½ months later when bony union was present (Fig. 6).

He was allowed full weight bearing 10 months after the injury. Figure 7 shows the appearance 1 year and 6 months after admission, and examination 6 months later showed full range of flexion, extension, and abduction, with limitation of internal rotation to 10 degrees.

The results in 3 cases in group III are summarized in Table III.

TABLE III.—RESULTS IN 3 CASES IN GROUP III

Treatment	Hips	Good	Fair	Poor
Traction and cast	2	1		1 (N)
Manipulation and cast	1			1 (N)
Total treated	3	1		2

(N)—Roentgenographic or pathologic evidence of aseptic necrosis of the epiphysis.

In the second patient, admitted 3 weeks after complete separation of the epiphysis, satisfactory reposition was not obtained after traction over a 5 week period. Density contrast between the epiphysis and the atrophied bone of the shaft on the roentgenogram at this time indicated necrosis of the epiphysis, and replacement by open operation was considered advisable.

The third patient, first seen 13 months after complete separation of the epiphysis, showed roentgenographic evidence of necrosis of the epiphysis on admission. Reposition by manipulation under anesthesia elsewhere was followed by nonunion after immobilization in the Whitman position in plaster for 3 months. Excision of the epiphysis and arthrodesis of the hip were done. The pathologic findings in this case have been reported elsewhere (18).

A summary of the results following treatment in the 3 groups is seen in Table IV.

TABLE IV.—RESULTS IN 3 GROUPS

	Hips No.	Good		Fair		Poor		Uncertain	
		No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
Group I	26	23	88.5			1	3.8	2	7.7
Group II	23	11	47.8	3	13.0	5	21.7	4	17.5
Group III	3	1	33.3			2	66.6		
Total	52	35	67.3	3	5.8	8	15.4	6	11.5

COMPLICATIONS AND SEQUELAE

No permanent limitation of motion of the knee was encountered following immobilization over periods up to 9 months. Knee function returned to normal after 2 to 4 months.

Genu valgum following stretching of the medial collateral ligament and capsule of the knee was an

occasional problem. This complication occurred in limbs subjected to prolonged heavy skin traction. Relief of spasm by general anesthesia seems advisable if not accomplished by skin traction after 8 to 10 days. Prolonged traction, when indicated, is maintained better by means of a threaded wire inserted through the distal metaphysis of the femur.

Progressive loss of motion and fibrous ankylosis of the hips occurred in 1 patient with bilateral involvement. Displacement was minimal on one side and moderate on the other. The result 4 years later was marked limitation of motion and advanced degenerative arthritis of both hip joints. Explanation of this unusual sequela is difficult. The articular cartilage became thinned and the shadow of the epiphyseal cortex on the roentgenogram became irregular, but both epiphyses underwent marked disuse atrophy comparable to that of the shafts which spoke against necrosis of the epiphyses. The marked stiffening of the joints with identical changes on both sides suggests a severe nonspecific inflammatory reaction as the cause of these changes.

Aseptic necrosis of the epiphysis was observed in 1 instance out of 29 patients with minimal displacement. Of 23 moderately displaced epiphyses in group II, aseptic necrosis was observed in 4. Of these, 3 showed evidence of necrosis of the epiphysis on admission, and in 1 case necrosis followed progressive displacement of the epiphysis in a limb inadequately protected by a nonweight bearing caliper brace. Necrosis occurred in 2 of the 3 epiphyses in group III following complete separation.

Infarction of the epiphysis in adolescent epiphysiolysis may be followed by early degenerative changes in the hip joint. Such changes lead to considerable disability. Knowledge of the pathologic changes in a joint with this sequela has been scanty. Necrosis of the epiphysis, after surgical reposition, is accepted as inevitable by some authors (16). They, as well as others, advocate prolonged protection of the epiphysis from weight bearing to prevent collapse of the head during the period of replacement of the necrotic bone. If the overlying articular cartilage remains alive, and no collapse takes place, good function might be expected. Such circumstances may explain the good results observed by these authors.

In adults, Axhausen and Bergmann (2), and Phemister have shown that articular cartilage overlying areas of bone infarction frequently becomes necrotic. Phemister has shown that necrotic cartilage undergoes replacement by fibrocartilage or in part by bone. Axhausen (1) showed experimentally and clinically that degenerative arthritis was a common sequel to necrosis of the cartilage on one side of a joint.

In a previous description (18) of the pathologic changes in the epiphysis of 2 cases included in the present report it was shown that in adolescence complete or partial necrosis of the articular cartilage may occur after infarction of an epiphysis. The articular cartilage in these cases was undergoing replacement by fibrocartilage and bone.

Preservation of the circulation to the epiphysis is therefore of importance if degenerative arthritis and poor joint function are to be avoided. Clinical observations of others support this contention (4, 25).

SUMMARY AND CONCLUSIONS

1. The methods employed, and the results in the treatment of 44 cases of adolescent epiphysiolysis in various stages of displacement are reported. Reposition of the epiphysis was not usually attempted, and was not accomplished in any case except in those in which there was recent complete separation of the epiphysis following sudden trauma.

2. Of 26 hips with minimal displacement of the epiphysis treated in group I, good function was obtained in 88.5 per cent following immobilization and protection of the affected hip until ossification of the capital epiphyseal growth cartilage took place.

3. Good function was obtained in 47.8 per cent of 23 hips with moderate displacement of the epiphysis in group II following the conservative plan of treatment outlined. Thirteen per cent resulted in fair function, and 21.7 per cent had poor results. In only 1 case, or 4.4 per cent of the total, could the poor result be attributed to treatment. Results in the remaining 17.5 per cent of the cases are not known.

4. Satisfactory replacement, a living epiphysis, and a normally functioning hip followed prolonged adhesive skin traction and immobilization in 1, or 33.3 per cent, of 3 cases in group III with complete separation. In 2 cases, poor results were due to necrosis of the epiphysis.

5. Epiphyseal necrosis may occur naturally in cases with minimal displacement. It is not uncommonly present in cases with moderate displacement first seen after bony union of the epiphysis has occurred. It is frequent following complete separation of the epiphysis due to sudden trauma.

6. Death of the epiphysis, as a complication following manipulative or surgical reposition of the epiphysis, is reported in a relatively high per-

centage of such cases in the literature. This disturbance was not a complication in this series of cases in which adequate conservative treatment was employed.

7. The methods used in the care of these patients are in contrast to manipulative or operative measures of treatment which increase the probability of interruption of the blood supply to the epiphysis. Long term evaluation of these divergent methods, with reference to late disability from traumatic arthritis, cannot be made until follow-up studies of representative series of such cases have been made 20 to 30 years after treatment.

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EDITORIALS

SURGERY
Gynecology and Obstetrics

FRANKLIN H. MARTIN
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MARCH, 1945

UNITED STATES ARMY MEDICAL CORPS

IN the September, 1944, issue of SURGERY, GYNECOLOGY AND OBSTETRICS appeared an editorial, "Organization of the Red Army Medical Corps," signed by Dr. Loyal Davis, who was until recently an officer in the Medical Corps, Army of the United States. Dr. Davis compares unfavorably the administrative organization of the Red Army Medical Corps and that of the United States Army. His thesis is, in brief, that the Surgeon General of the Red Army has a direct relationship and responsibility to General Staff; and that his Medical Corps is centralized into a single unit for which he determines policies and their application. In contrast, the Surgeon General of the United States Army is without direct General Staff representation or responsibility except as these may be had through the intermediary Services of Supply; the Medical Corps of the United States Army is so decentralized as to provide for what amounts in practice to an autonomous and separate Corps for the Air Force, and separate and independent Medical Corps in each theater of operations; that the Surgeon General's power is limited to "merely an agency for the procurement and distribution of supplies and personnel"; that in other respects his functions are advisory only, subordinate to nonmedical officers of the Army Service Forces, without power to deal directly with Chief Surgeons in theaters of operation until permission is obtained through the line of command.

Dr. Davis' editorial was forwarded by an interested physician to the Senators from Maryland, Millard Tydings and George L. Radcliffe, with an identical covering letter as follows:

"I commend to your attention the enclosed editorial by Dr. Loyal Davis concerning the 'Organization of the Red Army Medical Corps.' The editorial is badly entitled, since its subject matter deals largely with the U. S. Army Medical Corps, and constitutes an invidious comparison of our own with that of the Red Army. The difficulties which Dr. Davis so ably outlines have been presented to several Surgeons General of the Army, to the Chief of Staff, and to the Secretary of War, but no remedial action has been taken. Many physicians now serving in the U. S. Army Medical Corps and many other civilian physicians familiar with that Corps, either by previous service in, or present contact with it, completely share Dr. Davis' point of view. The difficulties enumerated do not lie with the Surgeon General but instead, as Dr. Davis points out, in his concluding sentence, in 'The fundamental anomalous relation of his office to the General Staff and the Army as a whole, which can be corrected only by the War Department.'

"I should be most interested to have your reaction to this problem and your opinion as to whether anything might be accomplished through Congressional discussion with the Secretary of War."

Copy of the editorial was also sent to General George Marshall, Chief of Staff, United States Army, and to the Honorable Henry L. Stimson, Secretary of War, with the following identical covering letter:

"I commend to your earnest attention the enclosed editorial by Dr. Loyal Davis, copied from SURGERY, GYNECOLOGY AND OBSTETRICS, one of the leading influential medical journals of this country. The point of view expressed by Dr. Davis is, I know, shared by many members of the U.S. Army Medical Corps and by civilian physicians."

On October 30, Senator Tydings replied as follows:

"I am in the office today for about an hour, after an absence of some two weeks because of speaking engagements throughout the State in connection with my campaign. I found your letter of the 23rd awaiting me, with the editorial by Dr. Loyal Davis, concerning the Army Medical Corps.

"Time does not permit me to read the article as carefully as I should like to at the moment, for I have two or three radio talks I must write, together with an accumulation of senatorial and political correspondence requiring my personal attention.

"I feel, however, that I have grasped the point made by him and I think it worthy of further examination. In the meantime, I am forwarding Dr. Davis' article on to the Secretary of War, believing that the points raised by Dr. Davis are worthy to be considered in order to give the greatest amount of efficiency to the Army Medical Corps.

"I hope something constructive may come out of this endeavor and I appreciate your letting me have the editorial by Dr. Davis."

And a few days later he courteously forwarded the following letter to himself from the Secretary of War:

"Thank you for sending me a copy of the editorial by Doctor Loyal Davis which I have noted and am returning in accordance with your request.

"As you know, we are constantly studying the efficiency of the administrative and operational aspects of the War Department with an aim to achieving greater efficiency. The problem raised concerning the Surgeon General and the medical mission is constantly under survey, and I know that the point of view raised in the editorial will be carefully considered in trying to achieve greater economics in the use of Medical Department personnel and facilities."

Senator Radcliffe sent two letters in reply as follows:

"I have been reading with very much interest, indeed, your letter of October 23, enclosing a copy of an editorial entitled 'Organization of the Red Army Medical Corps' by Dr. Loyal Davis.

"Since I am a layman, my views probably should not be very definite, but it seems to me that there is very much force in what you write me and in what Dr. Davis says in his editorial.

"All this brings back to my mind various discussions which I heard during and shortly after the first world war. You will recall of course Dr. Welch, Dr. Young, Dr. Baer, Dr. Stone, and many other of the outstanding physicians and surgeons of the Johns Hopkins Medical School took a very active part in the war and rendered invaluable service. I remember that several people stated that the situation was very anomalous when a man like Dr. William Welch, as prominent in medicine as any one in the world, should occupy a subordinate rôle, not in military medicine administration merely, but in other matters more technical. Rearrangements were made which eliminated most of the objections.

"I am very glad you wrote this letter to me and I am using it as a basis of some inquiries and discussion about the matter."

"I received today a letter from Judge Patterson in regard to the article on 'Organization of the Red Army Medical Corps.' He and Secretary Stimson are discussing this matter."

General Marshall referred the covering letter and Dr. Davis' editorial to the Surgeon General who, on November 6, replied as follows:

"Your letter and the inclosure of the editorial from SURGERY, GYNECOLOGY AND OBSTETRICS by Dr. Loyal Davis has been forwarded to me by General Marshall with the request that I acknowledge it. I expressed my evaluation of the editorial by pointing out that in my opinion the editorial probably expressed the feelings of the overwhelming majority of the 45,000 Medical Corps officers in the Army Medical Corps. In addition, I pointed out that the subject is of sufficient moment to warrant study since it is essential that all steps be explored which could possibly contribute to the more efficient utilization of Medical Department personnel and facilities.

"Thank you for your interest in calling this editorial and the problem which it raises to the attention of General Marshall."

There can be little doubt in the minds of doctors in or out of the military service, that the present organization of the Medical Corps of the United States Army is wholly unsatisfactory and should be changed. The marvel is that the Medical Corps, handicapped as it is by faulty organization, hampered as it is by medically uninstructed line officers, has accomplished so much. It could do much more. It is to be devoutly hoped that the ripple created by Dr. Davis' stone tossed into muddy

waters will become a tidal wave leading to critical study, review, and rapid change of a medically intolerable situation.

JOSEPH EARLE MOORE.

PLASMA

EXPERIENCE in the Mediterranean (North African) Theater of Operations embracing campaigns in Tunisia, Sicily, Italy and France, has afforded ample opportunity to evaluate the usage of plasma infusion in wounded and injured men. It was anticipated, immediately observed and has been subsequently confirmed that plasma is not a physiologic substitute for whole blood in the management of the seriously wounded and injured. Plasma can be considered a substitute only in so far as it can be shipped, stored, and made available in the combat zone where refrigeration, laboratory testing, and other safeguards that must surround blood transfusion cannot be provided. Even here it is a substitute only for the purpose of restoring or maintaining blood volume during the period of delay necessary to transportation and the starting of a whole blood transfusion.

The "recovery" from shock that follows plasma infusion affords a false sense of security to the doctor who administers it—particularly if he is not an experienced surgeon. It may encourage him to attempt operative surgery that the patient is not prepared to withstand. Restoration of blood pressure and volume flow before hemorrhage has ceased or under conditions in which it cannot be arrested immediately by surgical operation, leads to further loss of red cells and terminates in disaster. When surgery must be delayed it may be essential to keep the patient alive with plasma, but not to attempt to establish full circulatory compensation. A systolic blood pressure of about 85 millimeters has been designated as a safe compromise level. On reaching hospital where surgery is to be performed, blood and blood plasma are used in relative amounts of about three and one.

Plasma is looked upon as a first-aid measure for dire surgical emergencies, not as a safe or satisfactory therapeutic agent for hemorrhage. It is a supplement, not a substitute, for whole blood. Specific indications for its usage are found in the management of burns and a few other conditions in which only the plasma is lost from the circulation. Even in these instances, it appears that objections to the employment of whole blood have been exaggerated.

In the United States, a wide and sustained publicity campaign has been required to secure blood from voluntary donors for conversion into dried plasma to meet the requirements of the Army and Navy. Large overhead investments have been made in processing plants. This effort cannot be commended too highly; the needs have been met and thousands of lives saved.

However, a solemn word of warning is not amiss at this time. An attempt to project the use of plasma into the emergencies of civilian surgery as a substitute for whole blood, except as here defined, will exact a high price in human life. *This has happened many times under circumstances beyond control because of the exigencies of war.* It will also increase the cost of surgical care to an extraordinary degree by the unnecessary use of an innocuous but expensive and fashionable method of therapy. The "vitamine racket" can be made to appear a pale and small time affair in contrast.

EDWARD D. CHURCHILL,
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AMERICAN COLLEGE OF SURGEONS

1945 WAR SESSIONS DEFERRED

THE American College of Surgeons, as an aid to the war effort, has deferred its 1945 series of War Sessions at the request of the War Committee on Conventions of the Office of Defense Transportation for the curtailment of meetings until such time as the present emergency has passed and conditions have improved.

Plans had been completed for the February meetings in St. Louis, Louisville, Milwaukee, and Cleveland, because earlier indications were that sessions of a strictly educational nature, limited to relatively small local areas, and bearing upon military and civilian health, would be sanctioned by the committee. However, in a special communication which has been received by Dr. Malcolm T. MacEachern, associate director of the College, the secretary of the committee, Mr. R. H. Clare, wrote in part as follows:

"This Committee has reviewed your application and has decided that these War Sessions can reasonably be deferred because of the present critical transportation and housing situation. While we appreciate the contribution already made by the American College of Surgeons in discontinuing all national meetings, it is necessary to request this further curtailment of your activities at least until such time as we have passed the present emergency and conditions have improved. We will need your complete co-operation if the objectives of this Committee are to be attained and we are confident that we will receive your support."